



PATENT  
Customer No. 22,852  
Attorney Docket No. 3495.0010-20

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re Application of: )  
)  
Marc ALIZON et al. ) Group Art Unit: 1637  
)  
Application No.: 08/308,219 ) Examiner: Jeffrey Norman Fredman  
)  
Filed: September 19, 1994 ) Confirmation No.: 4832  
)  
For: DNA SEQUENCE OF THE LTR REGION OF HUMAN IMMUNODEFICIENCY  
VIRUS TYPE 1 (HIV-1) (as amended)

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Sir:

**REQUEST TO CORRECT INVENTORSHIP**

Pursuant to 37 C.F.R. § 1.48, applicants request that the inventorship in this application be corrected as follows.

Pursuant to 37 C.F.R. § 1.48 (c), please add the following inventors to this application:

Robert C. Gallo,  
Milkulas Popovic,  
Mangalasseril G. Sarngadharan,  
Solange Chamaret,  
Claudine Axler-Bin,  
Francoise Rey,  
Marie-Therese Nugeyre,  
Jacqueline Gruet,  
Charles Dauget,  
Willy Rozenbaum,  
Christine Rouzioux,  
Francoise Brun-Vezinet,  
Luc Montagnier,  
Jean-Claude Chermann,

06/06/2006 JADD01 00000001 08308219  
06 FC:1464 130.00 OP

**BEST AVAILABLE COPY**

Francoise Barre-Sinoussi, and  
Pierre Tiollais.

The addition of the above-named inventors is necessitated by amendment of the claims during prosecution of this application.

A statement from each person being added as an inventor that the addition is necessitated by amendment of the claims and that the inventorship error occurred without deceptive intent is enclosed.

A Declaration by each of the actual inventors is enclosed. One copy of the application is enclosed although each Declaration was attached to a copy of the application when it was executed. The duplicate copies of the application have been removed to reduce the size of the submission, but will be provided by applicants if the Examiner requires them.

The written consent of each of the assignees is enclosed.

A check for the required fee of \$130.00 under § 1.17(c) is enclosed.

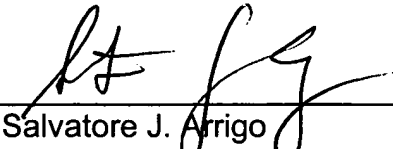
Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,  
GARRETT & DUNNER, L.L.P.

Dated: June 5, 2006

By: \_\_\_\_\_

  
Salvatore J. Arrigo  
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Telephone: 202-408-4160  
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## DECLARATION

As a below named inventor, I hereby declare that: my residence, post office address and citizenship are as stated below next to my name; I believe I am an original, first, and joint inventor of the subject matter of claims 25, 29, and 32, which is claimed and for which a patent is sought on the invention entitled: DNA SEQUENCE OF THE LTR REGION OF HUMAN IMMUNODEFICIENCY VIRUS TYPE 1 (HIV-1) the specification of which was filed on September 19, 1994, as United States Application No. 08/308,219 and Confirmation No. 4832.

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UNITED KINGDOM	84 23659	September 19, 1984	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
UNITED KINGDOM	83 24800	September 15, 1983	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO


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Full Name of First Inventor: Robert C. Gallo	Inventor's Signature 	Date May 31, '06
Residence 9100 Aldershot Drive, Bethesda, Maryland 20817-1902		Citizenship United States
Post Office Address 9100 Aldershot Drive, Bethesda, Maryland 20817-1902		
Full Name of Second Inventor Mikulas Popovic	Inventor's Signature	Date
Residence 9917 Holmhurst Road, Bethesda, Maryland 20817		Citizenship United States
Post Office Address 9917 Holmhurst Road, Bethesda, Maryland 20817		
Full Name of Third Inventor: Mangalasseril G. Sarngadharan	Inventor's Signature	Date
Residence 8422 Holly Leaf Drive, McLean, Virginia 22102-2224		Citizenship United States
Post Office Address 8422 Holly Leaf Drive, McLean, Virginia 22102-2224		
Full Name of Fourth Inventor: Solange Chamaret	Inventor's Signature	Date
Residence 138 boulevard Voltaire, 750M Paris, France		Citizenship French
Post Office Address 138 boulevard Voltaire, 750M Paris, France		
Full Name of Fifth Inventor: Claudine Axler-Blin	Inventor's Signature	Date
Residence 137 rue Lecourbe, 75015 Paris, France		Citizenship French
Post Office Address 137 rue Lecourbe, 75015 Paris, France		
Full Name of Sixth Inventor Francoise Rey	Inventor's Signature	Date
Residence 84 boulevard du Redon-Le Floucat-Allee des Pins, 13009 Marseille, France		Citizenship French
Post Office Address 84 boulevard du Redon-Le Floucat-Allee des Pins, 13009 Marseille, France		
Full Name of Seventh Inventor: Marie-Therese Nugeyre	Inventor's Signature	Date
Residence 92130 Issy-les-Moulineaux, France		Citizenship French
Post Office Address 92130 Issy-les-Moulineaux, France		
Full Name of Eighth Inventor Jacqueline Gruet (Deceased) Jacques Gruet (Legal Successor)	Inventor's Signature	Date
Residence Grue du Gué, 94240 L'Hay les Roses, France		Citizenship French
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Full Name of Ninth Inventor: Charles Dauguet	Inventor's Signature	Date
Residence 137 rue Lecourbe, 75015 Paris, France		Citizenship French
Post Office Address 137 rue Lecourbe, 75015 Paris, France		
Full Name of Tenth Inventor Willy Rozenbaum	Inventor's Signature	Date
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Post Office Address 20 rue de Sucy, 94430 Chennnevières-sur-Marne, France		
Full Name of Eleventh Inventor: Christine Rouzioux	Inventor's Signature	Date
Residence 21 rue de Dantzig, 75015 Paris, France		Citizenship French
Post Office Address 21 rue de Dantzig, 75015 Paris, France		
Full Name of Twelfth Inventor Francois Brun-Vezinet	Inventor's Signature	Date
Residence 24 boulevard Saint Germain, 75005 Paris, France		Citizenship French
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Full Name of Thirteenth Inventor: Luc Montagnier	Inventor's Signature	Date
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Post Office Address 104 de Capricorne, 50 rue d'Érevan, 92130 Issy les Moulineaux, Franch		
Full Name of Sixteenth Inventor Pierre Tiollais	Inventor's Signature	Date
Residence 16 rue de la Glaciere, 75013 Paris, France		Citizenship French
Post Office Address 16 rue de la Glaciere, 75013 Paris, France		

Full Name of Seventeenth Inventor: Marc Alizon	Inventor's Signature	Date
Residence 26 rue Censier, 75005 Paris, France		Citizenship French
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Full Name of Eighteenth Inventor Pierre Sonigo	Inventor's Signature	Date
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Residence 23 bis rue Cécile Dunant, 92140 Clahart, France		Citizenship United Kingdom
Post Office Address 23 bis rue Cécile Dunant, 92140 Clahart, France		
Full Name of Twenty-First Inventor: Oliver Danos	Inventor's Signature	Date
Residence 173 rue Saint Merry, 7730 Fontainebleau, France		Citizenship French
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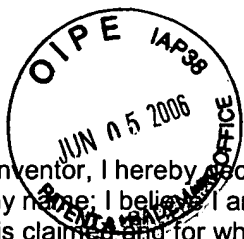
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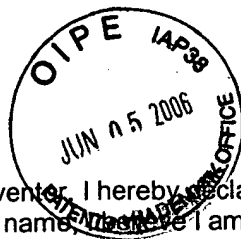
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FRANCE	84 16013	October 18, 1984	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
UNITED KINGDOM	84 23659	September 19, 1984	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
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Residence 8422 Holly Leaf Drive, McLean, Virginia 22102-2224		Citizenship United States
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Full Name of Fourth Inventor: Solange Chamaret	Inventor's Signature <i>S Chamaret</i>	Date 24-05-06
Residence 138 boulevard Voltaire, 750M Paris, France		Citizenship French
Post Office Address 138 boulevard Voltaire, 750M Paris, France		
Full Name of Fifth Inventor: Claudine Axler-Blin	Inventor's Signature	Date
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Full Name of Sixth Inventor Francoise Rey	Inventor's Signature	Date
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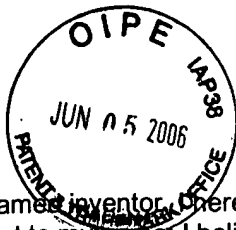
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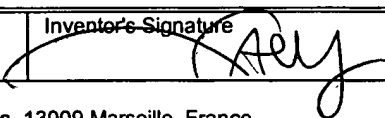
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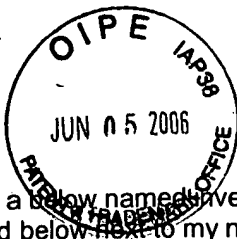
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Full Name of First Inventor: Robert C. Gallo	Inventor's Signature	Date
Residence 9100 Aldershot Drive, Bethesda, Maryland 20817-1902		Citizenship United States
Post Office Address 9100 Aldershot Drive, Bethesda, Maryland 20817-1902		
Full Name of Second Inventor Mikulas Popovic	Inventor's Signature	Date
Residence 9917 Holmhurst Road, Bethesda, Maryland 20817		Citizenship United States
Post Office Address 9917 Holmhurst Road, Bethesda, Maryland 20817		
Full Name of Third Inventor: Mangalasseril G. Samgadharan	Inventor's Signature	Date
Residence 8422 Holly Leaf Drive, McLean, Virginia 22102-2224		Citizenship United States
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Full Name of Fourth Inventor: Solange Chamaret	Inventor's Signature	Date
Residence 138 boulevard Voltaire, 750M Paris, France		Citizenship French
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Full Name of Fifth Inventor: Claudine Axler-Blin	Inventor's Signature	Date
Residence 137 rue Lecourbe, 75015 Paris, France		Citizenship French
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Full Name of Sixth Inventor Francoise Rey	Inventor's Signature	Date
Residence 84 boulevard du Redon-Le Floucat-Allee des Pins, 13009 Marseille, France		Citizenship French
Post Office Address 84 boulevard du Redon-Le Floucat-Allee des Pins, 13009 Marseille, France		
Full Name of Seventh Inventor: Marie-Therese Nugeyre	Inventor's Signature 	Date May 29 2006
Residence 92130 Issy-les-Moulineaux, France		Citizenship French
Post Office Address 92130 Issy-les-Moulineaux, France		
Full Name of Eighth Inventor Jacqueline Gruet (Deceased) Jacques Gruet (Legal Successor)	Inventor's Signature	Date
Residence Grue du Gué, 94240 L'Hay les Roses, France		Citizenship French
Post Office Address Grue du Gué, 94240 L'Hay les Roses, France		

Full Name of Ninth Inventor: Charles Dauguet	Inventor's Signature	Date
Residence 137 rue Lecourbe, 75015 Paris, France		Citizenship French
Post Office Address 137 rue Lecourbe, 75015 Paris, France		
Full Name of Tenth Inventor Willy Rozenbaum	Inventor's Signature	Date
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Full Name of Sixteenth Inventor Pierre Tiollais	Inventor's Signature	Date
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Full Name of Twenty-First Inventor: Oliver Danos	Inventor's Signature	Date
Residence 173 rue Saint Merry, 7730 Fontainebleau, France		Citizenship French
Post Office Address 173 rue Saint Merry, 7730 Fontainebleau, France		



## DECLARATION

I, JACQUELINE GRUEST, as the heir of JACQUELINE GRUEST, who is deceased, do hereby make the following declaration on her behalf:

As a below named inventor, I hereby declare that: my residence, post office address and citizenship are as stated below next to my name; I believe I am an original, first, and joint inventor of the subject matter, which is claimed and for which a patent is sought on the invention entitled: DNA SEQUENCE OF THE LTR REGION OF HUMAN IMMUNODEFICIENCY VIRUS TYPE 1 (HIV-1) the specification of which was filed on September 19, 1994, as United States Application No. 08/308,219 and Confirmation No. 4832.

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims. I acknowledge the duty to disclose information, which is material to patentability as defined in 37 CFR § 1.56.

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Country	Application Number	Date of Filing	Priority Claimed Under 35 U.S.C. 119
UNITED KINGDOM	84 29099	November 16, 1984	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
FRANCE	84 16013	October 18, 1984	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
UNITED KINGDOM	84 23659	September 19, 1984	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
UNITED KINGDOM	83 24800	September 15, 1983	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

I hereby claim the benefit under 35 U.S.C. § 119(e) of any United States provisional applications listed below:

Application Number	Date of Filing

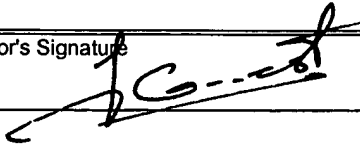
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Full Name of Eighth Inventor Jacqueline Gruet (Deceased) Jacques Gruet (Legal Successor)	Inventor's Signature 	Date 25.05.2006
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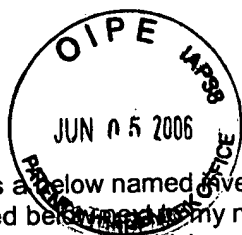
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Full Name of Ninth Inventor: Charles Dauguet	Inventor's Signature <i>Charles Dauguet</i>	Date 26 May 2006
Residence 137 rue Lecourbe, 75015 Paris, France		Citizenship French
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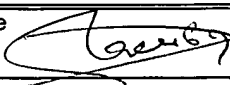
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Full Name of Eleventh Inventor: Christine Rouzioux	Inventor's Signature	Date
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Full Name of Twelfth Inventor Francois Brun-Vezinet	Inventor's Signature	Date
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Full Name of Twenty-First Inventor: Oliver Danos	Inventor's Signature	Date
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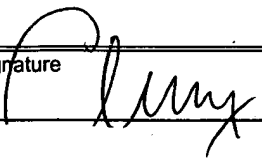
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Customer Number 22,852  
Attorney Docket No. 3495.0010-20

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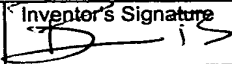

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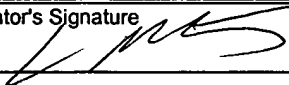
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UNITED KINGDOM	84 23659	September 19, 1984	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
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Full Name of Seventh Inventor: Marie-Therese Nugeyre	Inventor's Signature	Date
Residence 92130 Issy-les-Moulineaux, France		Citizenship French
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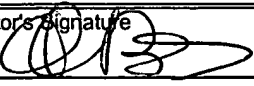
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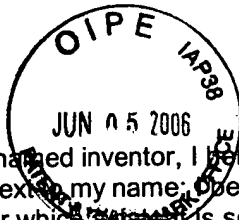
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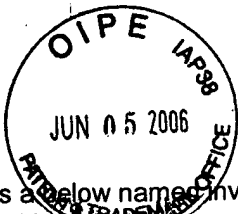
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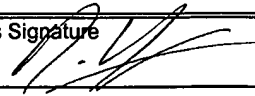
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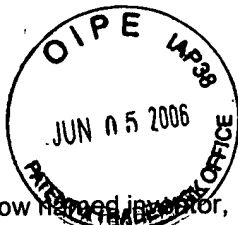
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Residence 9100 Aldershot Drive, Bethesda, Maryland 20817-1902		Citizenship United States
Post Office Address 9100 Aldershot Drive, Bethesda, Maryland 20817-1902		
Full Name of Second Inventor Mikulas Popovic	Inventor's Signature	Date
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Full Name of Seventeenth Inventor: Marc Alizon	Inventor's Signature 	Date 31.5.2006
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UNITED KINGDOM	84 23659	September 19, 1984	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
UNITED KINGDOM	83 24800	September 15, 1983	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

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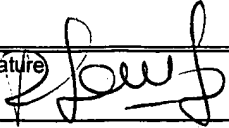
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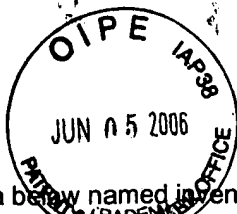
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Full Name of Nineteenth Inventor: Simon Wain-Hobson	Inventor's Signature <i>Simon Wain-Hobson</i>	Date <i>24 May 2006</i>
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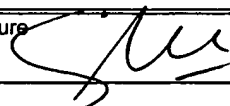
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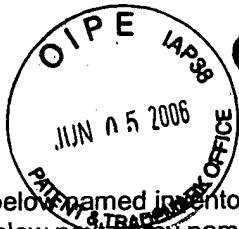
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Full Name of Nineteenth Inventor: Simon Wain-Hobson	Inventor's Signature	Date
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## DECLARATION

As a below-named inventor, I hereby declare that: my residence, post office address and citizenship are as stated below next to my name; I believe I am an original, first, and joint inventor of the subject matter, which is claimed and for which a patent is sought on the invention entitled: DNA SEQUENCE OF THE LTR REGION OF HUMAN IMMUNODEFICIENCY VIRUS TYPE 1 (HIV-1) the specification of which was filed on September 19, 1994, as United States Application No. 08/308,219 and Confirmation No. 4832.

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims. I acknowledge the duty to disclose information, which is material to patentability as defined in 37 CFR § 1.56.

I hereby claim foreign priority benefits under 35 U.S.C. § 119(a)-(d) or § 365(b) of any foreign application(s) for patent or inventor's certificate or § 365(a) of any PCT international application(s) designating at least one country other than the United States, listed below and have also identified below, any foreign application(s) for patent or inventor's certificate, or any PCT International application(s) having a filing date before that of the application(s) of which priority is claimed:

Country	Application Number	Date of Filing	Priority Claimed Under 35 U.S.C. 119
UNITED KINGDOM	84 29099	November 16, 1984	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
FRANCE	84 16013	October 18, 1984	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
UNITED KINGDOM	84 23659	September 19, 1984	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
UNITED KINGDOM	83 24800	September 15, 1983	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

I hereby claim the benefit under 35 U.S.C. § 119(e) of any United States provisional applications listed below:

Application Number	Date of Filing

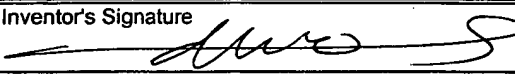
I hereby claim the benefit under 35 U.S.C. § 120 of any United States application(s) or § 365(c) of any PCT International application(s) designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application(s) in the manner provided by the first paragraph of 35 U.S.C. § 112, I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR § 1.56 which became available between the filing date of the prior application(s) and the national or PCT International filing date of this application:

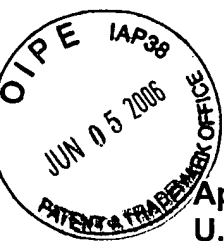
Application Number	Date of Filing	Status (Patented, Pending, Abandoned)
06/771,248	August 30, 1985	Abandoned
07/999,410	December 31, 1992	Pending
07/499,210	March 19, 1990	Pending
06/771,230	August 30, 1985	Abandoned
06/706,562	February 28, 1985	Abandoned
06/558,109	December 5, 1983	Abandoned

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

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Full Name of Twelfth Inventor Francois Brun-Vezinet	Inventor's Signature	Date
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**Application Data Sheet****U.S. Application No. 08/308,219****Filed: September 19, 1994****Attorney Docket No. 03495.0010-20000**

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**Application Information**

Application No.: 08/308/219  
Filing Date: 09/18/1994  
Title Line One: DNA Sequence of the LTR Region of Human  
Title Line Two: Immunodeficiency Virus Type 1 (HIV-1) (as amended)  
Total Drawing Sheets: 26  
Formal Drawings?: N/A  
Application Type: Utility  
Docket Number: 03495.0010-20000

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Representative Customer Number: 22,852

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### Domestic Priority Information

Application:	Continuity Type:	Parent Application:	Parent Filing Date:
This application	Division of	07/158,652	02/22/88
07/158,652	Division of	06/771,248	08/30/85
This application	Continuation-in-part of	07/999,410	12/31/92
07/999,410	Continuation of	07/499,210	03/19/90
07/499,210	Continuation of	06/771,230	08/30/95
06/771,230	Continuation-in-part of	06/706,562	02/28/85
06/706,562	Continuation-in-part of	06/558,109	12/05/83

### Foreign Priority Information

Country:	Application Number:	Filing Date:	Priority Claimed:
United Kingdom	84 29099	11/16/84	Yes
France	84 16013	10/18/84	Yes
United Kingdom	83 24800	09/15/83	Yes
United Kingdom	84 23659	09/19/84	Yes

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: )  
 ) Group Art Unit: 1637  
Marc Alizon et al. )  
 ) Examiner: Jeffrey N. Fredman  
Application No.: 08/308,219 )  
 ) Confirmation No.: 4832  
Filed: September 19, 1994 )  
 )  
For: DNA SEQUENCE OF THE LTR  
REGION OF HUMAN  
IMMUNODEFICIENCY VIRUS  
TYPE 1 (HIV-1)

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Sir:

**POWER OF ATTORNEY**

Applicants' Assignee hereby grants power of attorney to **FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P.** Customer Number 22,852, to transact all business in the Patent and Trademark Office connected therewith, and to receive the Letters Patent. Please also send all future correspondence concerning this application to Finnegan, Henderson, Farabow, Garrett & Dunner, L.L.P., Customer Number 22,852

The undersigned is authorized to sign this Power of Attorney.

Respectfully submitted,

Dated: JUNE 6, 2006

By: Jack Spiegel  
Name: JACK SPIEGEL (REG # 34,477)  
Title: SENIOR ADVISOR FOR TECHNOLOGY TRANSFER OPERATIONS  
Assignee: United States of America as  
represented by the Secretary of  
the Department of Health and  
Human Services



PATENT  
Customer No. 22,852  
Attorney Docket No. 3495.0010-20

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Marc Alizon et al.

Application No.: 08/308,219

Filed: September 19, 1994

For: DNA SEQUENCE OF THE LTR  
REGION OF HUMAN  
IMMUNODEFICIENCY VIRUS  
TYPE 1 (HIV-1)

)  
) Group Art Unit: 1637  
)  
) Examiner: Jeffrey N. Fredman  
)  
) Confirmation No.: 4832  
)  
)

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Sir:

**STATEMENT OF CHRISTINE ROUZIOUX**  
**(Being Added As An Inventor)**

I have read U.S. application Serial No. 08/308,219.

I am informed that I was not named as an inventor in application Serial No.  
08/308,219 when the application was filed in the U.S. Patent and Trademark Office.

I have been informed that the claims in U.S. application Serial No. 08/308,219  
have been amended by adding claims 17-22, 25, and 27-40 to the application.

I am informed that a copy of claims 17-22, 25, and 27-40 is attached hereto.

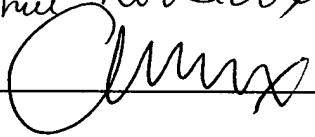
I have read claims 17-22, 25, and 27-40, which I am informed were added to  
U.S. application Serial No. 08/308,219 to claim previously unclaimed subject matter.

I understand that I am being added as an inventor to U.S. application Serial No. 08/308,219.

I have been informed that my addition as an inventor to U.S. application Serial No. 08/308,219 is necessitated by the amendment of the claims by adding claims 17-22, 25, and 27-40 to the application.

The inventorship error resulting from the amendment of the claims by adding claims 17-22, 25, and 27-40 to U.S. application Serial No. 08/308,219 occurred without deceptive intention on my part.

I hereby declare that all statements made of my own knowledge and belief are true and that all statements made on information and belief are believed to be true and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Christine Rozewsky  
By:   
Date: 30.05.2006

U.S. Patent Application No. 08/308,219

Filed: September 19, 1994

Inventors: Marc ALIZON et al.

Div. of 07/158,652 (02/22/88);

Div. of 06/771,248 (08/30/85);

CIP of 07/999,410 (12/31/92);

Cont. of 07/499,210 (03/19/90);

Cont of 06/771,230 (08/30/85);

CIP of 06/706,562 (02/28/85)'

CIP of 06/558,109 (12/5/83)

DI No.: 84-37

Our Reference: 03495.0010-20000

Pending Claims

17. A purified recombinant DNA of human immunodeficiency virus type 1 (HIV-1), wherein the DNA comprises the sequence:

8570	8580	8590	8600	8610
GGGGGACTGG	AAGGGCTAAT	TCACTCCCAA	CGAAGACAAG	ATATCCTTGA
8620	8630	8640	8650	8660
TCTGTGGATC	TACCACACAC	AAGGCTACTT	CCCTGATTGG	CAGAACTACA
8670	8680	8690	8700	8710
CACCAGGGCC	AGGGGTCAGA	TATCCACTGA	CCTTTGGATG	GTGCTACAAG
8720	8730	8740	8750	8760
CTAGTACCAG	TTGAGCCAGA	TAAGGTAGAA	GAGGCCAATA	AAGGAGAGAA
8770	8780	8790	8800	8810
CACCAGCTTG	TTACACCCTG	TGAGCCTGCA	TGGAATGGAT	GACCCTGAGA
8820	8830	8840	8850	8860
GAGAAGTGTT	AGAGTGGAGG	TTTGACAGCC	GCCTAGCATT	TCATCACGTG
8870	8880	8890	8900	8910
GCCCCGAGAGC	TGCATCCGGA	GTACTTCAAG	AACTGCTGAC	ATCGAGCTTG
8920	8930	8940	8950	8960
CTACAAGGGA	CTTTCCGCTG	GGGACTTTCC	AGGGAGGCGT	GGCCTGGGCG
8970	8980	8990	9000	9010
GAACTGGGGA	GTGGCGAGCC	CTCAGATGCT	GCATATAAGC	AGCTGCTTTT

9020	9030	9040	9050	9060
TGCCTGTACT	GGGTCTCTCT	GGTTAGACCA	GATTTGAGCC	TGGGAGCTCT
9070	9080	9090	9097	10
CTGGCTAACT	AGGGAACCCA	CTGCTTAAGC	CTCAATA	AAGCTTGCCT
20	30	40	50	60
TGAGTGCTTC	AAGTAGTGTG	TGCCCCGTCTG	TTGTGTGACT	CTGGTAACTA
70	80	90	100	110
GAGATCCCTC	AGACCCTTTT	AGTCAGTGTG	GAAAATCTCT	AGCAGTGGCG
120	130	140	150	159
CCCGAACAGG	GACTTGAAAG	CGAAAGGGAA	ACCAGAGGAG	CTCTCTCGA

18. The purified recombinant DNA of claim 17, wherein said nucleic acid is labeled with a label selected from the group consisting of a radioisotope, an enzyme, a fluorescent label, and a chromophore label.

19. A method of using the purified recombinant DNA of claim 17 for detecting the presence of HIV-1 RNA comprising:

- (a) providing a cell-free supernatant of a biological fluid comprising cells infected with HIV-1;
- (b) disrupting HIV-1 virions in the cell-free supernatant to release HIV-1 RNA; and
- (c) detecting the presence of HIV-1 RNA by contacting the HIV-1 RNA with the purified recombinant DNA of claim 17 and detecting hybridization between the HIV-1 RNA and the purified recombinant DNA.

20. The method of claim 19, wherein the biological fluid is blood.

21. A method of using the purified recombinant DNA of claim 18 for detecting the presence of HIV-1 RNA comprising:

(a) providing a cell-free supernatant of a biological fluid comprising cells infected with HIV-1;

(b) disrupting HIV-1 virions in the cell-free supernatant to release HIV-1 RNA; and

(c) detecting the presence of HIV-1 RNA by contacting the HIV-1 RNA with the purified recombinant DNA of claim 18 and detecting hybridization between the HIV-1 RNA and the purified recombinant DNA.

22. The method of claim 21, wherein the biological fluid is blood.

25. A method for detecting the presence of HIV-1 RNA comprising:

(a) providing a cell-free supernatant of a biological fluid comprising cells infected with HIV-1;

(b) disrupting HIV-1 virions in the cell-free supernatant to release HIV-1 RNA; and

(c) detecting the presence of HIV-1 RNA.

27. The method of claim 25, wherein the presence of HIV-1 RNA is detected by contacting the HIV-1 RNA with the DNA of claim 17 and detecting hybridization between the HIV-1 RNA and the purified recombinant DNA.

28. The method of claim 25, wherein the presence of HIV-1 RNA is detected by contacting the HIV-1 RNA with the DNA of claim 18 and detecting hybridization between the HIV-1 RNA and the purified recombinant DNA.

29. A method for preparing HIV-1 RNA for detecting the presence of HIV-1 RNA comprising:

- (a) providing a cell-free supernatant of a biological fluid comprising cells infected with HIV-1;
- (b) disrupting HIV-1 virions in the cell-free supernatant to release HIV-1 RNA.

30. The method of claim 29, further comprising detecting the presence of HIV-1 RNA by contacting the HIV-1 RNA with the DNA of claim 17 and detecting hybridization between the HIV-1 RNA and the purified recombinant DNA.

31. The method of claim 29, further comprising detecting the presence of HIV-1 RNA by contacting the HIV-1 RNA with the DNA of claim 18 and detecting hybridization between the HIV-1 RNA and the purified recombinant DNA.

32. A method for preparing HIV-1 RNA for detecting the presence of HIV-1 RNA comprising:

- (a) providing a cell-free supernatant of a biological fluid comprising cells infected with HIV-1;

(b) isolating HIV-1 virions from the cell-free supernatant; and

(c) disrupting the virions to release HIV-1 RNA.

33. The method of claim 32, further comprising detecting the presence of HIV-1 RNA by contacting the HIV-1 RNA with the DNA of claim 17 and detecting hybridization between the HIV-1 RNA and the purified recombinant DNA.

34. The method of claim 32, further comprising detecting the presence of HIV-1 RNA by contacting the HIV-1 RNA with the DNA of claim 18 and detecting hybridization between the HIV-1 RNA and the purified recombinant DNA.

35. A purified fragment of the recombinant DNA of claim 17, wherein said fragment comprises the sequence:

CTCAATAAAGCTTGCCTTG.

36. The purified fragment of claim 35, wherein said nucleic acid is labeled with a label selected from the group consisting of a radioisotope, an enzyme, a fluorescent label, and a chromophore label.

37. A method of using the purified fragment of claim 35 for detecting the presence of HIV-1 RNA comprising:

(a) providing a cell-free supernatant of a biological fluid comprising cells infected with HIV-1;

(b) disrupting HIV-1 virions in the cell-free supernatant to release HIV-1 RNA; and

(c) detecting the presence of HIV-1 RNA by contacting the HIV-1 RNA with the purified fragment of claim 35 and detecting hybridization between the HIV-1 RNA and the purified fragment.

38. The method of claim 37, wherein the biological fluid is blood.

39. A method of using the purified fragment of claim 36 for detecting the presence of HIV-1 RNA comprising:

(a) providing a cell-free supernatant of a biological fluid comprising cells infected with HIV-1;

(b) disrupting HIV-1 virions in the cell-free supernatant to release HIV-1 RNA; and

(c) detecting the presence of HIV-1 RNA by contacting the HIV-1 RNA with the purified fragment of claim 36 and detecting hybridization between the HIV-1 RNA and the purified fragment.

40. The method of claim 39, wherein the biological fluid is blood.



PATENT  
Customer No. 22,852  
Attorney Docket No. 3495.0010-20

UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: )  
 ) Group Art Unit: 1637  
Marc Alizon et al. )  
 ) Examiner: Jeffrey N. Fredman  
Application No.: 08/308,219 )  
 ) Confirmation No.: 4832  
Filed: September 19, 1994 )  
 )  
For: DNA SEQUENCE OF THE LTR  
REGION OF HUMAN  
IMMUNODEFICIENCY VIRUS  
TYPE 1 (HIV-1)

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Sir:

**STATEMENT OF LUC MONTAGNIER**  
**(Being Added As An Inventor)**

I have read U.S. application Serial No. 08/308,219.

I am informed that I was not named as an inventor in application Serial No.  
08/308,219 when the application was filed in the U.S. Patent and Trademark Office.

I have been informed that the claims in U.S. application Serial No. 08/308,219  
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I hereby declare that all statements made of my own knowledge and belief are true and that all statements made on information and belief are believed to be true and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

By: 

Date: May 24 2006

U.S. Patent Application No. 08/308,219

Filed: September 19, 1994

Inventors: Marc ALIZON et al.

Div. of 07/158,652 (02/22/88);

Div. of 06/771,248 (08/30/85);

CIP of 07/999,410 (12/31/92);

Cont. of 07/499,210 (03/19/90);

Cont of 06/771,230 (08/30/85);

CIP of 06/706,562 (02/28/85)'

CIP of 06/558,109 (12/5/83)

DI No.: 84-37

Our Reference: 03495.0010-20000

Pending Claims

17. A purified recombinant DNA of human immunodeficiency virus type 1 (HIV-1), wherein the DNA comprises the sequence:

8570	8580	8590	8600	8610
GGGGGACTGG	AAGGGCTAAT	TCACTCCCAA	CGAAGACAAG	ATATCCTTGA
8620	8630	8640	8650	8660
TCTGTGGATC	TACCACACAC	AAGGCTACTT	CCCTGATTGG	CAGAACTACA
8670	8680	8690	8700	8710
CACCAGGGCC	AGGGGTCAGA	TATCCACTGA	CCTTTGGATG	GTGCTACAAG
8720	8730	8740	8750	8760
CTAGTACCAG	TTGAGCCAGA	TAAGGTAGAA	GAGGCCAATA	AAGGAGAGAA
8770	8780	8790	8800	8810
CACCAGCTTG	TTACACCCTG	TGAGCCTGCA	TGGAATGGAT	GACCCTGAGA
8820	8830	8840	8850	8860
GAGAAGTGTT	AGAGTGGAGG	TTTGACAGCC	GCCTAGCATT	TCATCACGTG
8870	8880	8890	8900	8910
GCCCGAGAGC	TGCATCCGGA	GTA CTTCAAG	AACTGCTGAC	ATCGAGCTTG
8920	8930	8940	8950	8960
CTACAAGGGA	CTTTCCGCTG	GGGACTTTCC	AGGGAGGCGT	GGCCTGGGCG
8970	8980	8990	9000	9010
GAAGTGGGGA	GTGGCGAGCC	CTCAGATGCT	GCATATAAGC	AGCTGCTTTT

9020	9030	9040	9050	9060
TGCCTGTACT	GGGTCTCTCT	GGTTAGACCA	GATTTGAGCC	TGGGAGCTCT
9070	9080	9090	9097	10
CTGGCTAACT	AGGGAACCCA	CTGCTTAAGC	CTCAATA	AAGCTTGCCT
20	30	40	50	60
TGAGTGCTTC	AAGTAGTGTG	TGCCCCGTCTG	TTGTGTGACT	CTGGTAACTA
70	80	90	100	110
GAGATCCCTC	AGACCCTTTT	AGTCAGTGTG	GAAAATCTCT	AGCAGTGGCG
120	130	140	150	159
CCCGAACAGG	GACTTGAAAG	CGAAAGGGAA	ACCAGAGGAG	CTCTCTCGA

18. The purified recombinant DNA of claim 17, wherein said nucleic acid is labeled with a label selected from the group consisting of a radioisotope, an enzyme, a fluorescent label, and a chromophore label.

19. A method of using the purified recombinant DNA of claim 17 for detecting the presence of HIV-1 RNA comprising:

- (a) providing a cell-free supernatant of a biological fluid comprising cells infected with HIV-1;
- (b) disrupting HIV-1 virions in the cell-free supernatant to release HIV-1 RNA; and
- (c) detecting the presence of HIV-1 RNA by contacting the HIV-1 RNA with the purified recombinant DNA of claim 17 and detecting hybridization between the HIV-1 RNA and the purified recombinant DNA.

20. The method of claim 19, wherein the biological fluid is blood.

21. A method of using the purified recombinant DNA of claim 18 for detecting the presence of HIV-1 RNA comprising:

- (a) providing a cell-free supernatant of a biological fluid comprising cells infected with HIV-1;
- (b) disrupting HIV-1 virions in the cell-free supernatant to release HIV-1 RNA; and
- (c) detecting the presence of HIV-1 RNA by contacting the HIV-1 RNA with the purified recombinant DNA of claim 18 and detecting hybridization between the HIV-1 RNA and the purified recombinant DNA.

22. The method of claim 21, wherein the biological fluid is blood.

25. A method for detecting the presence of HIV-1 RNA comprising:

- (a) providing a cell-free supernatant of a biological fluid comprising cells infected with HIV-1;
- (b) disrupting HIV-1 virions in the cell-free supernatant to release HIV-1 RNA; and
- (c) detecting the presence of HIV-1 RNA.

27. The method of claim 25, wherein the presence of HIV-1 RNA is detected by contacting the HIV-1 RNA with the DNA of claim 17 and detecting hybridization between the HIV-1 RNA and the purified recombinant DNA.

28. The method of claim 25, wherein the presence of HIV-1 RNA is detected by contacting the HIV-1 RNA with the DNA of claim 18 and detecting hybridization between the HIV-1 RNA and the purified recombinant DNA.

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HIV-1 RNA comprising:

(a) providing a cell-free supernatant of a biological fluid comprising cells infected with HIV-1;

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30. The method of claim 29, further comprising detecting the presence of HIV-1 RNA by contacting the HIV-1 RNA with the DNA of claim 17 and detecting hybridization between the HIV-1 RNA and the purified recombinant DNA.

31. The method of claim 29, further comprising detecting the presence of HIV-1 RNA by contacting the HIV-1 RNA with the DNA of claim 18 and detecting hybridization between the HIV-1 RNA and the purified recombinant DNA.

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HIV-1 RNA comprising:

(a) providing a cell-free supernatant of a biological fluid comprising cells infected with HIV-1;

(b) isolating HIV-1 virions from the cell-free supernatant; and

(c) disrupting the virions to release HIV-1 RNA.

33. The method of claim 32, further comprising detecting the presence of HIV-1 RNA by contacting the HIV-1 RNA with the DNA of claim 17 and detecting hybridization between the HIV-1 RNA and the purified recombinant DNA.

34. The method of claim 32, further comprising detecting the presence of HIV-1 RNA by contacting the HIV-1 RNA with the DNA of claim 18 and detecting hybridization between the HIV-1 RNA and the purified recombinant DNA.

35. A purified fragment of the recombinant DNA of claim 17, wherein said fragment comprises the sequence:  
CTCAATAAAGCTTGCCTTG.

36. The purified fragment of claim 35, wherein said nucleic acid is labeled with a label selected from the group consisting of a radioisotope, an enzyme, a fluorescent label, and a chromophore label.

37. A method of using the purified fragment of claim 35 for detecting the presence of HIV-1 RNA comprising:

(a) providing a cell-free supernatant of a biological fluid comprising cells infected with HIV-1;

(b) disrupting HIV-1 virions in the cell-free supernatant to release HIV-1 RNA; and

(c) detecting the presence of HIV-1 RNA by contacting the HIV-1 RNA with the purified fragment of claim 35 and detecting hybridization between the HIV-1 RNA and the purified fragment.

38. The method of claim 37, wherein the biological fluid is blood.

39. A method of using the purified fragment of claim 36 for detecting the presence of HIV-1 RNA comprising:

(a) providing a cell-free supernatant of a biological fluid comprising cells infected with HIV-1;

(b) disrupting HIV-1 virions in the cell-free supernatant to release HIV-1 RNA; and

(c) detecting the presence of HIV-1 RNA by contacting the HIV-1 RNA with the purified fragment of claim 36 and detecting hybridization between the HIV-1 RNA and the purified fragment.

40. The method of claim 39, wherein the biological fluid is blood.



PATENT  
Customer No. 22,852  
Attorney Docket No. 3495.0010-20

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: )  
 ) Group Art Unit: 1637  
Marc Alizon et al. )  
 ) Examiner: Jeffrey N. Fredman  
Application No.: 08/308,219 )  
 ) Confirmation No.: 4832  
Filed: September 19, 1994 )  
 )  
For: DNA SEQUENCE OF THE LTR  
REGION OF HUMAN  
IMMUNODEFICIENCY VIRUS  
TYPE 1 (HIV-1)

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Sir:

**STATEMENT OF JEAN-CLAUDE CHERMANN**  
**(Being Added As An Inventor)**

I have read U.S. application Serial No. 08/308,219.

I am informed that I was not named as an inventor in application Serial No.  
08/308,219 when the application was filed in the U.S. Patent and Trademark Office.

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have been amended by adding claims 17-22, 25, and 27-40 to the application.

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By: Jean. Claude Chermusany

Date: May 26 . 06

U.S. Patent Application No. 08/308,219  
Filed: September 19, 1994  
Inventors: Marc ALIZON et al.  
Div. of 07/158,652 (02/22/88);  
Div. of 06/771,248 (08/30/85);  
CIP of 07/999,410 (12/31/92);  
Cont. of 07/499,210 (03/19/90);  
Cont of 06/771,230 (08/30/85);  
CIP of 06/706,562 (02/28/85)'  
CIP of 06/558,109 (12/5/83)  
DI No.: 84-37  
Our Reference: 03495.0010-20000

Pending Claims

17. A purified recombinant DNA of human immunodeficiency virus type 1 (HIV-1), wherein the DNA comprises the sequence:

8570	8580	8590	8600	8610
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8670	8680	8690	8700	8710
CACCAGGGCC	AGGGGTCAGA	TATCCACTGA	CCTTTGGATG	GTGCTACAAG
8720	8730	8740	8750	8760
CTAGTACCAG	TTGAGCCAGA	TAAGGTAGAA	GAGGCCAATA	AAGGAGAGAA
8770	8780	8790	8800	8810
CACCAGCTTG	TTACACCCTG	TGAGCCTGCA	TGGAATGGAT	GACCCTGAGA
8820	8830	8840	8850	8860
GAGAAGTGTT	AGAGTGGAGG	TTTGACAGCC	GCCTAGCATT	TCATCACGTG
8870	8880	8890	8900	8910
GCCCCGAGAGC	TGCATCCGGA	GTACTTCAAG	AACTGCTGAC	ATCGAGCTTG
8920	8930	8940	8950	8960
CTACAAGGGA	CTTTCCGCTG	GGGACTTTCC	AGGGAGGCGT	GGCCTGGGCG
8970	8980	8990	9000	9010
GAACTGGGGA	GTGGCGAGCC	CTCAGATGCT	GCATATAAGC	AGCTGCTTTT

9020	9030	9040	9050	9060
TGCCTGTACT	GGGTCTCTCT	GGTTAGACCA	GATTTGAGCC	TGGGAGCTCT
9070	9080	9090	9097	10
CTGGCTAACT	AGGGAACCCA	CTGCTTAAGC	CTCAATA	AAGCTTGCCT
20	30	40	50	60
TGAGTGCTTC	AAGTAGTGTG	TGCCCCGTCTG	TTGTGTGACT	CTGGTAACTA
70	80	90	100	110
GAGATCCCTC	AGACCCTTTT	AGTCAGTGTG	GAAAATCTCT	AGCAGTGGCG
120	130	140	150	159
CCCGAACAGG	GACTTGAAAG	CGAAAGGGAA	ACCAGAGGAG	CTCTCTCGA

18. The purified recombinant DNA of claim 17, wherein said nucleic acid is labeled with a label selected from the group consisting of a radioisotope, an enzyme, a fluorescent label, and a chromophore label.

19. A method of using the purified recombinant DNA of claim 17 for detecting the presence of HIV-1 RNA comprising:

- (a) providing a cell-free supernatant of a biological fluid comprising cells infected with HIV-1;
- (b) disrupting HIV-1 virions in the cell-free supernatant to release HIV-1 RNA; and
- (c) detecting the presence of HIV-1 RNA by contacting the HIV-1 RNA with the purified recombinant DNA of claim 17 and detecting hybridization between the HIV-1 RNA and the purified recombinant DNA.

20. The method of claim 19, wherein the biological fluid is blood.

21. A method of using the purified recombinant DNA of claim 18 for detecting the presence of HIV-1 RNA comprising:

(a) providing a cell-free supernatant of a biological fluid comprising cells infected with HIV-1;

(b) disrupting HIV-1 virions in the cell-free supernatant to release HIV-1 RNA; and

(c) detecting the presence of HIV-1 RNA by contacting the HIV-1 RNA with the purified recombinant DNA of claim 18 and detecting hybridization between the HIV-1 RNA and the purified recombinant DNA.

22. The method of claim 21, wherein the biological fluid is blood.

25. A method for detecting the presence of HIV-1 RNA comprising:

(a) providing a cell-free supernatant of a biological fluid comprising cells infected with HIV-1;

(b) disrupting HIV-1 virions in the cell-free supernatant to release HIV-1 RNA; and

(c) detecting the presence of HIV-1 RNA.

27. The method of claim 25, wherein the presence of HIV-1 RNA is detected by contacting the HIV-1 RNA with the DNA of claim 17 and detecting hybridization between the HIV-1 RNA and the purified recombinant DNA.

28. The method of claim 25, wherein the presence of HIV-1 RNA is detected by contacting the HIV-1 RNA with the DNA of claim 18 and detecting hybridization between the HIV-1 RNA and the purified recombinant DNA.

29. A method for preparing HIV-1 RNA for detecting the presence of

HIV-1 RNA comprising:

(a) providing a cell-free supernatant of a biological fluid comprising cells infected with HIV-1;

(b) disrupting HIV-1 virions in the cell-free supernatant to release HIV-1 RNA.

30. The method of claim 29, further comprising detecting the presence of HIV-1 RNA by contacting the HIV-1 RNA with the DNA of claim 17 and detecting hybridization between the HIV-1 RNA and the purified recombinant DNA.

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32. A method for preparing HIV-1 RNA for detecting the presence of

HIV-1 RNA comprising:

(a) providing a cell-free supernatant of a biological fluid comprising cells infected with HIV-1;

(b) isolating HIV-1 virions from the cell-free supernatant; and

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33. The method of claim 32, further comprising detecting the presence of HIV-1 RNA by contacting the HIV-1 RNA with the DNA of claim 17 and detecting hybridization between the HIV-1 RNA and the purified recombinant DNA.

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35. A purified fragment of the recombinant DNA of claim 17, wherein said fragment comprises the sequence:  
CTCAATAAAGCTTGCCTTG.

36. The purified fragment of claim 35, wherein said nucleic acid is labeled with a label selected from the group consisting of a radioisotope, an enzyme, a fluorescent label, and a chromophore label.

37. A method of using the purified fragment of claim 35 for detecting the presence of HIV-1 RNA comprising:

(a) providing a cell-free supernatant of a biological fluid comprising cells infected with HIV-1;

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38. The method of claim 37, wherein the biological fluid is blood.

39. A method of using the purified fragment of claim 36 for detecting the presence of HIV-1 RNA comprising:

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PATENT  
Customer No. 22,852  
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TYPE 1 (HIV-1)

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Sir:

**STATEMENT OF FRANÇOISE BARRE-SINOUSS**  
**(Being Added As An Inventor)**

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By:  \_\_\_\_\_

Date: 05.24.2006

U.S. Patent Application No. 08/308,219

Filed: September 19, 1994

Inventors: Marc ALIZON et al.

Div. of 07/158,652 (02/22/88);

Div. of 06/771,248 (08/30/85);

CIP of 07/999,410 (12/31/92);

Cont. of 07/499,210 (03/19/90);

Cont of 06/771,230 (08/30/85);

CIP of 06/706,562 (02/28/85)'

CIP of 06/558,109 (12/5/83)

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8770	8780	8790	8800	8810
CACCAGCTTG	TTACACCCTG	TGAGCCTGCA	TGGAATGGAT	GACCCCTGAGA
8820	8830	8840	8850	8860
GAGAAGTGTT	AGAGTGGAGG	TTTGACAGCC	GCCTAGCATT	TCATCACGTG
8870	8880	8890	8900	8910
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8920	8930	8940	8950	8960
CTACAAGGGA	CTTTCCGCTG	GGGACTTTCC	AGGGAGGCGT	GGCCTGGGCG
8970	8980	8990	9000	9010
GAACTGGGGA	GTGGCGAGCC	CTCAGATGCT	GCATATAAGC	AGCTGCTTTT

9020	9030	9040	9050	9060
TGCCTGTACT	GGGTCTCTCT	GGTTAGACCA	GATTTGAGCC	TGGGAGCTCT
9070	9080	9090	9097	10
CTGGCTAACT	AGGGAACCCA	CTGCTTAAGC	CTCAATA	AAGCTTGCCT
20	30	40	50	60
TGAGTGCTTC	AAGTAGTGTG	TGCCCCGTCTG	TTGTGTGACT	CTGGTAACTA
70	80	90	100	110
GAGATCCCTC	AGACCCTTTT	AGTCAGTGTG	GAAAATCTCT	AGCAGTGGCG
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- (b) disrupting HIV-1 virions in the cell-free supernatant to release HIV-1 RNA; and
- (c) detecting the presence of HIV-1 RNA by contacting the HIV-1 RNA with the purified recombinant DNA of claim 17 and detecting hybridization between the HIV-1 RNA and the purified recombinant DNA.

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28. The method of claim 25, wherein the presence of HIV-1 RNA is detected by contacting the HIV-1 RNA with the DNA of claim 18 and detecting hybridization between the HIV-1 RNA and the purified recombinant DNA.

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- (a) providing a cell-free supernatant of a biological fluid comprising cells infected with HIV-1;
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- (a) providing a cell-free supernatant of a biological fluid comprising cells infected with HIV-1;
- (b) disrupting HIV-1 virions in the cell-free supernatant to release HIV-1 RNA; and
- (c) detecting the presence of HIV-1 RNA by contacting the HIV-1 RNA with the purified recombinant DNA of claim 18 and detecting hybridization between the HIV-1 RNA and the purified recombinant DNA.

22. The method of claim 21, wherein the biological fluid is blood.

25. A method for detecting the presence of HIV-1 RNA comprising:

- (a) providing a cell-free supernatant of a biological fluid comprising cells infected with HIV-1;
- (b) disrupting HIV-1 virions in the cell-free supernatant to release HIV-1 RNA; and
- (c) detecting the presence of HIV-1 RNA.

27. The method of claim 25, wherein the presence of HIV-1 RNA is detected by contacting the HIV-1 RNA with the DNA of claim 17 and detecting hybridization between the HIV-1 RNA and the purified recombinant DNA.

(b) isolating HIV-1 virions from the cell-free supernatant; and

(c) disrupting the virions to release HIV-1 RNA.

33. The method of claim 32, further comprising detecting the presence of HIV-1 RNA by contacting the HIV-1 RNA with the DNA of claim 17 and detecting hybridization between the HIV-1 RNA and the purified recombinant DNA.

34. The method of claim 32, further comprising detecting the presence of HIV-1 RNA by contacting the HIV-1 RNA with the DNA of claim 18 and detecting hybridization between the HIV-1 RNA and the purified recombinant DNA.

35. A purified fragment of the recombinant DNA of claim 17, wherein said fragment comprises the sequence:  
CTCAATAAAGCTTGCCTTG.

36. The purified fragment of claim 35, wherein said nucleic acid is labeled with a label selected from the group consisting of a radioisotope, an enzyme, a fluorescent label, and a chromophore label.

37. A method of using the purified fragment of claim 35 for detecting the presence of HIV-1 RNA comprising:

(a) providing a cell-free supernatant of a biological fluid comprising cells infected with HIV-1;

(b) disrupting HIV-1 virions in the cell-free supernatant to release HIV-1 RNA; and

(c) detecting the presence of HIV-1 RNA by contacting the HIV-1 RNA with the purified fragment of claim 35 and detecting hybridization between the HIV-1 RNA and the purified fragment.

38. The method of claim 37, wherein the biological fluid is blood.

39. A method of using the purified fragment of claim 36 for detecting the presence of HIV-1 RNA comprising:

(a) providing a cell-free supernatant of a biological fluid comprising cells infected with HIV-1;

(b) disrupting HIV-1 virions in the cell-free supernatant to release HIV-1 RNA; and

(c) detecting the presence of HIV-1 RNA by contacting the HIV-1 RNA with the purified fragment of claim 36 and detecting hybridization between the HIV-1 RNA and the purified fragment.

40. The method of claim 39, wherein the biological fluid is blood.



PATENT  
Customer No. 22,852  
Attorney Docket No. 3495.0010-20

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: )  
 ) Group Art Unit: 1637  
Marc Alizon et al. )  
 ) Examiner: Jeffrey N. Fredman  
Application No.: 08/308,219 )  
 ) Confirmation No.: 4832  
Filed: September 19, 1994 )  
 )  
For: DNA SEQUENCE OF THE LTR  
REGION OF HUMAN  
IMMUNODEFICIENCY VIRUS  
TYPE 1 (HIV-1)

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Sir:

**STATEMENT OF PIERRE TIOLLAIS**  
**(Being Added As An Inventor)**

I have read U.S. application Serial No. 08/308,219.

I am informed that I was not named as an inventor in application Serial No.  
08/308,219 when the application was filed in the U.S. Patent and Trademark Office.

I have been informed that the claims in U.S. application Serial No. 08/308,219  
have been amended by adding claims 17-22, 25, and 27-40 to the application.

I am informed that a copy of claims 17-22, 25, and 27-40 is attached hereto.

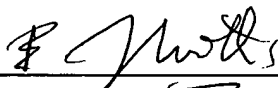
I have read claims 17-22, 25, and 27-40, which I am informed were added to  
U.S. application Serial No. 08/308,219 to claim previously unclaimed subject matter.

I understand that I am being added as an inventor to U.S. application Serial No. 08/308,219.

I have been informed that my addition as an inventor to U.S. application Serial No. 08/308,219 is necessitated by the amendment of the claims by adding claims 17-22, 25, and 27-40 to the application.

The inventorship error resulting from the amendment of the claims by adding claims 17-22, 25, and 27-40 to U.S. application Serial No. 08/308,219 occurred without deceptive intention on my part.

I hereby declare that all statements made of my own knowledge and belief are true and that all statements made on information and belief are believed to be true and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

By: 

Date: 24 mai 06

U.S. Patent Application No. 08/308,219

Filed: September 19, 1994

Inventors: Marc ALIZON et al.

Div. of 07/158,652 (02/22/88);

Div. of 06/771,248 (08/30/85);

CIP of 07/999,410 (12/31/92);

Cont. of 07/499,210 (03/19/90);

Cont of 06/771,230 (08/30/85);

CIP of 06/706,562 (02/28/85)'

CIP of 06/558,109 (12/5/83)

DI No.: 84-37

Our Reference: 03495.0010-20000

Pending Claims

17. A purified recombinant DNA of human immunodeficiency virus type 1 (HIV-1), wherein the DNA comprises the sequence:

8570	8580	8590	8600	8610
GGGGGACTGG	AAGGGCTAAT	TCACTCCCAA	CGAAGACAAG	ATATCCTTGA
8620	8630	8640	8650	8660
TCTGTGGATC	TACCACACAC	AAGGCTACTT	CCCTGATTGG	CAGAACTACA
8670	8680	8690	8700	8710
CACCAGGGCC	AGGGGTCAGA	TATCCACTGA	CCTTTGGATG	GTGCTACAAG
8720	8730	8740	8750	8760
CTAGTACCAG	TTGAGCCAGA	TAAGGTAGAA	GAGGCCAATA	AAGGAGAGAA
8770	8780	8790	8800	8810
CACCAGCTTG	TTACACCCTG	TGAGCCTGCA	TGGAATGGAT	GACCCTGAGA
8820	8830	8840	8850	8860
GAGAAGTGTT	AGAGTGGAGG	TTTGACAGCC	GCCTAGCATT	TCATCACGTG
8870	8880	8890	8900	8910
GCCCGAGAGC	TGCATCCGGA	GTACTTCAAG	AACTGCTGAC	ATCGAGCTTG
8920	8930	8940	8950	8960
CTACAAGGGA	CTTTCCGCTG	GGGACTTTCC	AGGGAGGCGT	GGCCTGGGCG
8970	8980	8990	9000	9010
GAACTGGGGA	GTGGCGAGCC	CTCAGATGCT	GCATATAAGC	AGCTGCTTTT

9020	9030	9040	9050	9060
TGCCTGTACT	GGGTCTCTCT	GGTTAGACCA	GATTTGAGCC	TGGGAGCTCT
9070	9080	9090	9097	10
CTGGCTAACT	AGGGAACCCA	CTGCTTAAGC	CTCAATA	AAGCTTGCCCT
20	30	40	50	60
TGAGTGCTTC	AAGTAGTGTG	TGCCCCGTCTG	TTGTGTGACT	CTGGTAACTA
70	80	90	100	110
GAGATCCCTC	AGACCCTTTT	AGTCAGTGTG	GAAAATCTCT	AGCAGTGGCG
120	130	140	150	159
CCCGAACAGG	GACTTGAAAG	CGAAAGGGAA	ACCAGAGGAG	CTCTCTCGA

18. The purified recombinant DNA of claim 17, wherein said nucleic acid is labeled with a label selected from the group consisting of a radioisotope, an enzyme, a fluorescent label, and a chromophore label.

19. A method of using the purified recombinant DNA of claim 17 for detecting the presence of HIV-1 RNA comprising:

- (a) providing a cell-free supernatant of a biological fluid comprising cells infected with HIV-1;
- (b) disrupting HIV-1 virions in the cell-free supernatant to release HIV-1 RNA; and
- (c) detecting the presence of HIV-1 RNA by contacting the HIV-1 RNA with the purified recombinant DNA of claim 17 and detecting hybridization between the HIV-1 RNA and the purified recombinant DNA.

20. The method of claim 19, wherein the biological fluid is blood.

21. A method of using the purified recombinant DNA of claim 18 for detecting the presence of HIV-1 RNA comprising:

- (a) providing a cell-free supernatant of a biological fluid comprising cells infected with HIV-1;
- (b) disrupting HIV-1 virions in the cell-free supernatant to release HIV-1 RNA; and
- (c) detecting the presence of HIV-1 RNA by contacting the HIV-1 RNA with the purified recombinant DNA of claim 18 and detecting hybridization between the HIV-1 RNA and the purified recombinant DNA.

22. The method of claim 21, wherein the biological fluid is blood.

25. A method for detecting the presence of HIV-1 RNA comprising:

- (a) providing a cell-free supernatant of a biological fluid comprising cells infected with HIV-1;
- (b) disrupting HIV-1 virions in the cell-free supernatant to release HIV-1 RNA; and
- (c) detecting the presence of HIV-1 RNA.

27. The method of claim 25, wherein the presence of HIV-1 RNA is detected by contacting the HIV-1 RNA with the DNA of claim 17 and detecting hybridization between the HIV-1 RNA and the purified recombinant DNA.

28. The method of claim 25, wherein the presence of HIV-1 RNA is detected by contacting the HIV-1 RNA with the DNA of claim 18 and detecting hybridization between the HIV-1 RNA and the purified recombinant DNA.

29. A method for preparing HIV-1 RNA for detecting the presence of

HIV-1 RNA comprising:

(a) providing a cell-free supernatant of a biological fluid comprising cells infected with HIV-1;

(b) disrupting HIV-1 virions in the cell-free supernatant to release HIV-1 RNA.

30. The method of claim 29, further comprising detecting the presence of HIV-1 RNA by contacting the HIV-1 RNA with the DNA of claim 17 and detecting hybridization between the HIV-1 RNA and the purified recombinant DNA.

31. The method of claim 29, further comprising detecting the presence of HIV-1 RNA by contacting the HIV-1 RNA with the DNA of claim 18 and detecting hybridization between the HIV-1 RNA and the purified recombinant DNA.

32. A method for preparing HIV-1 RNA for detecting the presence of

HIV-1 RNA comprising:

(a) providing a cell-free supernatant of a biological fluid comprising cells infected with HIV-1;

(b) isolating HIV-1 virions from the cell-free supernatant; and

(c) disrupting the virions to release HIV-1 RNA.

33. The method of claim 32, further comprising detecting the presence of HIV-1 RNA by contacting the HIV-1 RNA with the DNA of claim 17 and detecting hybridization between the HIV-1 RNA and the purified recombinant DNA.

34. The method of claim 32, further comprising detecting the presence of HIV-1 RNA by contacting the HIV-1 RNA with the DNA of claim 18 and detecting hybridization between the HIV-1 RNA and the purified recombinant DNA.

35. A purified fragment of the recombinant DNA of claim 17, wherein said fragment comprises the sequence:  
CTCAATAAAGCTTGCCTTG.

36. The purified fragment of claim 35, wherein said nucleic acid is labeled with a label selected from the group consisting of a radioisotope, an enzyme, a fluorescent label, and a chromophore label.

37. A method of using the purified fragment of claim 35 for detecting the presence of HIV-1 RNA comprising:

(a) providing a cell-free supernatant of a biological fluid comprising cells infected with HIV-1;

(b) disrupting HIV-1 virions in the cell-free supernatant to release HIV-1 RNA; and

(c) detecting the presence of HIV-1 RNA by contacting the HIV-1 RNA with the purified fragment of claim 35 and detecting hybridization between the HIV-1 RNA and the purified fragment.

38. The method of claim 37, wherein the biological fluid is blood.

39. A method of using the purified fragment of claim 36 for detecting the presence of HIV-1 RNA comprising:

(a) providing a cell-free supernatant of a biological fluid comprising cells infected with HIV-1;

(b) disrupting HIV-1 virions in the cell-free supernatant to release HIV-1 RNA; and

(c) detecting the presence of HIV-1 RNA by contacting the HIV-1 RNA with the purified fragment of claim 36 and detecting hybridization between the HIV-1 RNA and the purified fragment.

40. The method of claim 39, wherein the biological fluid is blood.



PATENT  
Customer No. 22,852  
Attorney Docket No. 3495.0010-20

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: )  
Marc Alizon et al. ) Group Art Unit: 1637  
Application No.: 08/308,219 ) Examiner: Jeffrey N. Fredman  
Filed: September 19, 1994 ) Confirmation No.: 4832  
For: DNA SEQUENCE OF THE LTR )  
REGION OF HUMAN )  
IMMUNODEFICIENCY VIRUS )  
TYPE 1 (HIV-1) )

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Sir:

**STATEMENT OF ROBERT C. GALLO**  
**(Being Added As An Inventor)**

I have read U.S. application Serial No. 08/308,219.

I am informed that I was not named as an inventor in application Serial No. 08/308,219 when the application was filed in the U.S. Patent and Trademark Office.

I have been informed that the claims in U.S. application Serial No. 08/308,219 have been amended by adding claims 25, 29, and 32 to the application.

I am informed that a copy of claims 25, 29, and 32 is attached hereto.

I have read claims 25, 29, and 32, which I am informed were added to U.S. application Serial No. 08/308,219 to claim previously unclaimed subject matter.

I understand that I am being added as an inventor to U.S. application Serial No. 08/308,219.

I have been informed that my addition as an inventor to U.S. application Serial No. 08/308,219 is necessitated by the amendment of the claims by adding 25, 29, and 32 to the application.

The inventorship error resulting from the amendment of the claims by adding claims 25, 29, and 32 to U.S. application Serial No. 08/308,219 occurred without deceptive intention on my part.

I hereby declare that all statements made of my own knowledge and belief are true and that all statements made on information and belief are believed to be true and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

By: Robert C. Gallo

Date: May 31, 06

U.S. Patent Application No. 08/308,219  
Filed: September 19, 1994  
Inventors: Marc ALIZON et al.  
Div. of 07/158,652 (02/22/88);  
Div. of 06/771,248 (08/30/85);  
CIP of 07/999,410 (12/31/92);  
Cont. of 07/499,210 (03/19/90);  
Cont of 06/771,230 (08/30/85);  
CIP of 06/706,562 (02/28/85)'  
CIP of 06/558,109 (12/5/83)  
DI No.: 84-37  
Our Reference: 03495.0010-20000

25. A method for detecting the presence of HIV-1 RNA comprising:

- (a) providing a cell-free supernatant of a biological fluid comprising cells infected with HIV-1;
- (b) disrupting HIV-1 virions in the cell-free supernatant to release HIV-1 RNA; and
- (c) detecting the presence of HIV-1 RNA.

29. A method for preparing HIV-1 RNA for detecting the presence of HIV-1 RNA comprising:

- (a) providing a cell-free supernatant of a biological fluid comprising cells infected with HIV-1;
- (b) disrupting HIV-1 virions in the cell-free supernatant to release HIV-1 RNA.

32. A method for preparing HIV-1 RNA for detecting the presence of HIV-1 RNA comprising:

- (a) providing a cell-free supernatant of a biological fluid comprising cells infected with HIV-1;

(b) isolating HIV-1 virions from the cell-free supernatant; and

(c) disrupting the virions to release HIV-1 RNA.



PATENT  
Customer No. 22,852  
Attorney Docket No. 3495.0010-20

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: )  
 ) Group Art Unit: 1637  
Marc Alizon et al. )  
 ) Examiner: Jeffrey N. Fredman  
Application No.: 08/308,219 )  
 ) Confirmation No.: 4832  
Filed: September 19, 1994 )  
 )  
For: DNA SEQUENCE OF THE LTR  
REGION OF HUMAN  
IMMUNODEFICIENCY VIRUS  
TYPE 1 (HIV-1)

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Sir:

**STATEMENT OF MIKULAS POPOVIC**  
**(Being Added As An Inventor)**

I have read U.S. application Serial No. 08/308,219.

I am informed that I was not named as an inventor in application Serial No.  
08/308,219 when the application was filed in the U.S. Patent and Trademark Office.

I have been informed that the claims in U.S. application Serial No. 08/308,219  
have been amended by adding claims 25, 29, and 32 to the application.

I am informed that a copy of claims 25, 29, and 32 is attached hereto.

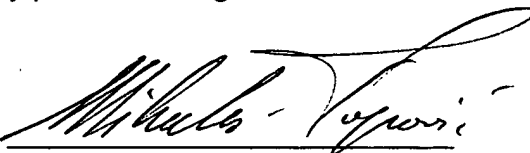
I have read claims 25, 29, and 32, which I am informed were added to U.S.  
application Serial No. 08/308,219 to claim previously unclaimed subject matter.

I understand that I am being added as an inventor to U.S. application Serial No. 08/308,219.

I have been informed that my addition as an inventor to U.S. application Serial No. 08/308,219 is necessitated by the amendment of the claims by adding 25, 29, and 32 to the application.

The inventorship error resulting from the amendment of the claims by adding claims 25, 29, and 32 to U.S. application Serial No. 08/308,219 occurred without deceptive intention on my part.

I hereby declare that all statements made of my own knowledge and belief are true and that all statements made on information and belief are believed to be true and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

By: 

Date: June 1, 2006

U.S. Patent Application No. 08/308,219  
Filed: September 19, 1994  
Inventors: Marc ALIZON et al.  
Div. of 07/158,652 (02/22/88);  
Div. of 06/771,248 (08/30/85);  
CIP of 07/999,410 (12/31/92);  
Cont. of 07/499,210 (03/19/90);  
Cont of 06/771,230 (08/30/85);  
CIP of 06/706,562 (02/28/85);  
CIP of 06/558,109 (12/5/83)  
DI No.: 84-37  
Our Reference: 03495.0010-20000

25. A method for detecting the presence of HIV-1 RNA comprising:

- (a) providing a cell-free supernatant of a biological fluid comprising cells infected with HIV-1;
- (b) disrupting HIV-1 virions in the cell-free supernatant to release HIV-1 RNA; and
- (c) detecting the presence of HIV-1 RNA.

29. A method for preparing HIV-1 RNA for detecting the presence of HIV-1 RNA comprising:

- (a) providing a cell-free supernatant of a biological fluid comprising cells infected with HIV-1;
- (b) disrupting HIV-1 virions in the cell-free supernatant to release HIV-1 RNA.

32. A method for preparing HIV-1 RNA for detecting the presence of HIV-1 RNA comprising:

- (a) providing a cell-free supernatant of a biological fluid comprising cells infected with HIV-1;

(b) isolating HIV-1 virions from the cell-free supernatant; and

(c) disrupting the virions to release HIV-1 RNA.



PATENT  
Customer No. 22,852  
Attorney Docket No. 3495.0010-20

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: )  
Marc Alizon et al. ) Group Art Unit: 1637  
Application No.: 08/308,219 ) Examiner: Jeffrey N. Fredman  
Filed: September 19, 1994 ) Confirmation No.: 4832  
For: DNA SEQUENCE OF THE LTR )  
REGION OF HUMAN )  
IMMUNODEFICIENCY VIRUS )  
TYPE 1 (HIV-1)

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Sir:

**STATEMENT OF MANGALASSERIL G. SARNGADHARAN**  
**(Being Added As An Inventor)**

I have read U.S. application Serial No. 08/308,219.

I am informed that I was not named as an inventor in application Serial No. 08/308,219 when the application was filed in the U.S. Patent and Trademark Office.

I have been informed that the claims in U.S. application Serial No. 08/308,219 have been amended by adding claims 25, 29, and 32 to the application.

I am informed that a copy of claims 25, 29, and 32 is attached hereto.

I have read claims 25, 29, and 32, which I am informed were added to U.S. application Serial No. 08/308,219 to claim previously unclaimed subject matter.

I understand that I am being added as an inventor to U.S. application Serial No. 08/308,219.

I have been informed that my addition as an inventor to U.S. application Serial No. 08/308,219 is necessitated by the amendment of the claims by adding 25, 29, and 32 to the application.

The inventorship error resulting from the amendment of the claims by adding claims 25, 29, and 32 to U.S. application Serial No. 08/308,219 occurred without deceptive intention on my part.

I hereby declare that all statements made of my own knowledge and belief are true and that all statements made on information and belief are believed to be true and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

By: Mangalasseri G. Sarnagadharan

Date: June 4, 2006

U.S. Patent Application No. 08/308,219  
Filed: September 19, 1994  
Inventors: Marc ALIZON et al.  
Div. of 07/158,652 (02/22/88);  
Div. of 06/771,248 (08/30/85);  
CIP of 07/999,410 (12/31/92);  
Cont. of 07/499,210 (03/19/90);  
Cont of 06/771,230 (08/30/85);  
CIP of 06/706,562 (02/28/85)'  
CIP of 06/558,109 (12/5/83)  
DI No.: 84-37  
Our Reference: 03495.0010-20000

25. A method for detecting the presence of HIV-1 RNA comprising:

- (a) providing a cell-free supernatant of a biological fluid comprising cells infected with HIV-1;
- (b) disrupting HIV-1 virions in the cell-free supernatant to release HIV-1 RNA; and
- (c) detecting the presence of HIV-1 RNA.

29. A method for preparing HIV-1 RNA for detecting the presence of HIV-1 RNA comprising:

- (a) providing a cell-free supernatant of a biological fluid comprising cells infected with HIV-1;
- (b) disrupting HIV-1 virions in the cell-free supernatant to release HIV-1 RNA.

32. A method for preparing HIV-1 RNA for detecting the presence of HIV-1 RNA comprising:

- (a) providing a cell-free supernatant of a biological fluid comprising cells infected with HIV-1;

(b) isolating HIV-1 virions from the cell-free supernatant; and

(c) disrupting the virions to release HIV-1 RNA.



PATENT  
Customer No. 22,852  
Attorney Docket No. 3495.0010-20

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Marc Alizon et al.

Application No.: 08/308,219

Filed: September 19, 1994

For: DNA SEQUENCE OF THE LTR  
REGION OF HUMAN  
IMMUNODEFICIENCY VIRUS  
TYPE 1 (HIV-1)

)  
) Group Art Unit: 1637  
)  
) Examiner: Jeffrey N. Fredman  
)  
) Confirmation No.: 4832  
)  
)

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Sir:

**CONSENT OF ASSIGNEE THE UNITED STATES OF AMERICA  
TO AMENDMENT OF INVENTORSHIP**

The United States of America as represented by the Secretary of the Department of Health and Human Services, having its principal place of business at 900 Rockville Pike, Bethesda, Maryland 20892, as an Assignee of the above-identified application, does hereby consent to amendment of inventorship from the inventive entity:

Marc Alizon  
Pierre Sonigo  
Simon Wain-Hobson  
Stewart Cole  
Oliver Danos

to the inventive entity:

Robert C. Gallo  
Mikulas Popovic  
Mangalasseril G. Sarngadharan  
Solange Chamaret  
Claudine Axler-Blin  
Françoise Rey  
Marie-Therese Nugeyre  
Jacqueline Gruet  
Charles Dauguet  
Willy Rozenbaum  
Christine Rouzioux  
François Brun-Vezinet  
Luc Montagnier  
Jean-Claude Chermann  
Françoise Barre-Sinoussi  
Pierre Tiollais  
Marc Alizon  
Pierre Sonigo  
Simon Wain-Hobson  
Stewart Cole  
Oliver Danos

The undersigned is authorized to act on behalf of the Assignee, the United States of America as represented by the Secretary of the Department of Health and Human Services.

I hereby declare that all statements made of my own knowledge and belief are true and that all statements made on information and belief are believed to be true and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Respectfully submitted,

By: Jack Spiegel  
Name: JACK SPIEGEL (REG# 34,477)  
Title: SENIOR ADVISOR FOR TECHNOLOGY TRANSFER OPERATIONS  
For Assignee: The United States of America  
as represented by the  
Secretary of the Department of  
Health and Human Services.

Dated: JUNE 5, 2006

1110249

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: )  
Marc Alizon et al. ) Group Art Unit: 1637  
Application No.: 08/308,219 ) Examiner: Jeffrey N. Fredman  
Filed: September 19, 1994 ) Confirmation No.: 4832  
For: DNA SEQUENCE OF THE LTR )  
REGION OF HUMAN )  
IMMUNODEFICIENCY VIRUS )  
TYPE 1 (HIV-1) )

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Sir:

**CONSENT OF ASSIGNEE INSTITUT PASTEUR  
TO AMENDMENT OF INVENTORSHIP**

Institut Pasteur, duly organized under the laws of France and having its principal place of business at 28, rue du Docteur Roux, 75724 Paris Cedex 15, France, as an Assignee of the above-identified application, does hereby consent to amendment of inventorship from the inventive entity:

Marc Alizon  
Pierre Sonigo  
Simon Wain-Hobson  
Stewart Cole  
Oliver Danos

to the inventive entity:

Solange Chamaret  
Claudine Axler-Blin  
Françoise Rey  
Marie-Therese Nugeyre  
Jacqueline Gruet  
Charles Dauguet  
Willy Rozenbaum  
Christine Rouzioux  
François Brun-Vezinet  
Luc Montagnier  
Jean-Claude Chermann  
Françoise Barre-Sinoussi  
Pierre Tiollais  
Marc Alizon  
Pierre Sonigo  
Simon Wain-Hobson  
Stewart Cole  
Oliver Danos  
Robert C. Gallo  
Mikulas Popovic  
Mangalasseril G. Sarngadharan

The undersigned is authorized to act on behalf of the Assignee, Institut Pasteur.

I hereby declare that all statements made of my own knowledge and belief are true and that all statements made on information and belief are believed to be true and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Respectfully submitted,

*A. Dautry*

By: \_\_\_\_\_  
Name: Alice Dautry  
Title: President  
For Assignee: Institut Pasteur

Dated: \_\_\_\_\_

*June 1<sup>st</sup>, 2006*



PATENT  
Customer No. 22,852  
Attorney Docket No. 3495.0010-20

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: )  
 ) Group Art Unit: 1637  
Marc Alizon et al. )  
 ) Examiner: Jeffrey N. Fredman  
Application No.: 08/308,219 )  
 ) Confirmation No.: 4832  
Filed: September 19,1994 )  
 )  
For: DNA SEQUENCE OF THE LTR  
REGION OF HUMAN  
IMMUNODEFICIENCY VIRUS  
TYPE 1 (HIV-1)

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Sir:

**STATEMENT OF SOLANGE CHAMARET**  
**(Being Added As An Inventor)**

I have read U.S. application Serial No. 08/308,219.

I am informed that I was not named as an inventor in application Serial No.  
08/308,219 when the application was filed in the U.S. Patent and Trademark Office.

I have been informed that the claims in U.S. application Serial No. 08/308,219  
have been amended by adding claims 17-22, 25, and 27-40 to the application.

I am informed that a copy of claims 17-22, 25, and 27-40 is attached hereto.

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I hereby declare that all statements made of my own knowledge and belief are true and that all statements made on information and belief are believed to be true and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

By: S. Hamare

Date: 24-05-2008

U.S. Patent Application No. 08/308,219

Filed: September 19, 1994

Inventors: Marc ALIZON et al.

Div. of 07/158,652 (02/22/88);

Div. of 06/771,248 (08/30/85);

CIP of 07/999,410 (12/31/92);

Cont. of 07/499,210 (03/19/90);

Cont of 06/771,230 (08/30/85);

CIP of 06/706,562 (02/28/85)'

CIP of 06/558,109 (12/5/83)

DI No.: 84-37

Our Reference: 03495.0010-20000

Pending Claims

17. A purified recombinant DNA of human immunodeficiency virus type 1 (HIV-1), wherein the DNA comprises the sequence:

8570	8580	8590	8600	8610
GGGGGACTGG	AAGGGCTAAT	TCACTCCCAA	CGAAGACAAG	ATATCCTTGA
8620	8630	8640	8650	8660
TCTGTGGATC	TACCACACAC	AAGGCTACTT	CCCTGATTGG	CAGAACTACA
8670	8680	8690	8700	8710
CACCAGGGCC	AGGGGTCAGA	TATCCACTGA	CCTTTGGATG	GTGCTACAAG
8720	8730	8740	8750	8760
CTAGTACCAG	TTGAGCCAGA	TAAGGTAGAA	GAGGCCAATA	AAGGAGAGAA
8770	8780	8790	8800	8810
CACCAGCTTG	TTACACCCTG	TGAGCCTGCA	TGGAATGGAT	GACCCTGAGA
8820	8830	8840	8850	8860
GAGAAGTGTT	AGAGTGGAGG	TTTGACAGCC	GCCTAGCATT	TCATCACGTG
8870	8880	8890	8900	8910
GCCCGAGAGC	TGCATCCGGA	GTA CTTCAAG	AACTGCTGAC	ATCGAGCTTG
8920	8930	8940	8950	8960
CTACAAGGGA	CTTTCCGCTG	GGGACTTTCC	AGGGAGGCGT	GGCCTGGGCG
8970	8980	8990	9000	9010
GAAGTGGGGA	GTGGCGAGCC	CTCAGATGCT	GCATATAAGC	AGCTGCTTTT

9020	9030	9040	9050	9060
TGCCTGTACT	GGGTCTCTCT	GGTTAGACCA	GATTTGAGCC	TGGGAGCTCT
9070	9080	9090	9097	10
CTGGCTAACT	AGGGAACCCA	CTGCTTAAGC	CTCAATA	AAGCTTGCCT
20	30	40	50	60
TGAGTGCTTC	AAGTAGTGTG	TGCCCCGTCTG	TTGTGTGACT	CTGGTAACTA
70	80	90	100	110
GAGATCCCTC	AGACCCTTTT	AGTCAGTGTG	GAAAATCTCT	AGCAGTGGCG
120	130	140	150	159
CCCGAACAGG	GACTTGAAAG	CGAAAGGGAA	ACCAGAGGAG	CTCTCTCGA

18. The purified recombinant DNA of claim 17, wherein said nucleic acid is labeled with a label selected from the group consisting of a radioisotope, an enzyme, a fluorescent label, and a chromophore label.

19. A method of using the purified recombinant DNA of claim 17 for detecting the presence of HIV-1 RNA comprising:

- (a) providing a cell-free supernatant of a biological fluid comprising cells infected with HIV-1;
- (b) disrupting HIV-1 virions in the cell-free supernatant to release HIV-1 RNA; and
- (c) detecting the presence of HIV-1 RNA by contacting the HIV-1 RNA with the purified recombinant DNA of claim 17 and detecting hybridization between the HIV-1 RNA and the purified recombinant DNA.

20. The method of claim 19, wherein the biological fluid is blood.

21. A method of using the purified recombinant DNA of claim 18 for detecting the presence of HIV-1 RNA comprising:

- (a) providing a cell-free supernatant of a biological fluid comprising cells infected with HIV-1;
- (b) disrupting HIV-1 virions in the cell-free supernatant to release HIV-1 RNA; and
- (c) detecting the presence of HIV-1 RNA by contacting the HIV-1 RNA with the purified recombinant DNA of claim 18 and detecting hybridization between the HIV-1 RNA and the purified recombinant DNA.

22. The method of claim 21, wherein the biological fluid is blood.

25. A method for detecting the presence of HIV-1 RNA comprising:

- (a) providing a cell-free supernatant of a biological fluid comprising cells infected with HIV-1;
- (b) disrupting HIV-1 virions in the cell-free supernatant to release HIV-1 RNA; and
- (c) detecting the presence of HIV-1 RNA.

27. The method of claim 25, wherein the presence of HIV-1 RNA is detected by contacting the HIV-1 RNA with the DNA of claim 17 and detecting hybridization between the HIV-1 RNA and the purified recombinant DNA.

28. The method of claim 25, wherein the presence of HIV-1 RNA is detected by contacting the HIV-1 RNA with the DNA of claim 18 and detecting hybridization between the HIV-1 RNA and the purified recombinant DNA.

29. A method for preparing HIV-1 RNA for detecting the presence of HIV-1 RNA comprising:

- (a) providing a cell-free supernatant of a biological fluid comprising cells infected with HIV-1;
- (b) disrupting HIV-1 virions in the cell-free supernatant to release HIV-1 RNA.

30. The method of claim 29, further comprising detecting the presence of HIV-1 RNA by contacting the HIV-1 RNA with the DNA of claim 17 and detecting hybridization between the HIV-1 RNA and the purified recombinant DNA.

31. The method of claim 29, further comprising detecting the presence of HIV-1 RNA by contacting the HIV-1 RNA with the DNA of claim 18 and detecting hybridization between the HIV-1 RNA and the purified recombinant DNA.

32. A method for preparing HIV-1 RNA for detecting the presence of HIV-1 RNA comprising:

- (a) providing a cell-free supernatant of a biological fluid comprising cells infected with HIV-1;

(b) isolating HIV-1 virions from the cell-free supernatant; and

(c) disrupting the virions to release HIV-1 RNA.

33. The method of claim 32, further comprising detecting the presence of HIV-1 RNA by contacting the HIV-1 RNA with the DNA of claim 17 and detecting hybridization between the HIV-1 RNA and the purified recombinant DNA.

34. The method of claim 32, further comprising detecting the presence of HIV-1 RNA by contacting the HIV-1 RNA with the DNA of claim 18 and detecting hybridization between the HIV-1 RNA and the purified recombinant DNA.

35. A purified fragment of the recombinant DNA of claim 17, wherein said fragment comprises the sequence:  
CTCAATAAAGCTTGCCTTG.

36. The purified fragment of claim 35, wherein said nucleic acid is labeled with a label selected from the group consisting of a radioisotope, an enzyme, a fluorescent label, and a chromophore label.

37. A method of using the purified fragment of claim 35 for detecting the presence of HIV-1 RNA comprising:

(a) providing a cell-free supernatant of a biological fluid comprising cells infected with HIV-1;

(b) disrupting HIV-1 virions in the cell-free supernatant to release HIV-1 RNA; and

(c) detecting the presence of HIV-1 RNA by contacting the HIV-1 RNA with the purified fragment of claim 35 and detecting hybridization between the HIV-1 RNA and the purified fragment.

38. The method of claim 37, wherein the biological fluid is blood.

39. A method of using the purified fragment of claim 36 for detecting the presence of HIV-1 RNA comprising:

(a) providing a cell-free supernatant of a biological fluid comprising cells infected with HIV-1;

(b) disrupting HIV-1 virions in the cell-free supernatant to release HIV-1 RNA; and

(c) detecting the presence of HIV-1 RNA by contacting the HIV-1 RNA with the purified fragment of claim 36 and detecting hybridization between the HIV-1 RNA and the purified fragment.

40. The method of claim 39, wherein the biological fluid is blood.



PATENT  
Customer No. 22,852  
Attorney Docket No. 3495.0010-20

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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Marc Alizon et al. ) Group Art Unit: 1637  
Application No.: 08/308,219 ) Examiner: Jeffrey N. Fredman  
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IMMUNODEFICIENCY VIRUS )  
TYPE 1 (HIV-1) )

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Sir:

**STATEMENT OF CLAUDINE AXLER-BLIN**  
**(Being Added As An Inventor)**

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By: Claudine Axler-Blin

Date: 26 May 2006

U.S. Patent Application No. 08/308,219

Filed: September 19, 1994

Inventors: Marc ALIZON et al.

Div. of 07/158,652 (02/22/88);

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8670	8680	8690	8700	8710
CACCAGGGCC	AGGGGTCAGA	TATCCACTGA	CCTTTGGATG	GTGCTACAAG
8720	8730	8740	8750	8760
CTAGTACCAG	TTGAGCCAGA	TAAGGTAGAA	GAGGCCAATA	AAGGAGAGAA
8770	8780	8790	8800	8810
CACCAGCTTG	TTACACCCTG	TGAGCCTGCA	TGGAATGGAT	GACCCTGAGA
8820	8830	8840	8850	8860
GAGAAGTGTT	AGAGTGGAGG	TTTGACAGCC	GCCTAGCATT	TCATCACGTG
8870	8880	8890	8900	8910
GCCCGAGAGC	TGCATCCGGA	GTA CTTC AAG	AACTGCTGAC	ATCGAGCTTG
8920	8930	8940	8950	8960
CTACAAGGGA	CTTTCCGCTG	GGGACTTTCC	AGGGAGGCGT	GGCCTGGGCG
8970	8980	8990	9000	9010
GAAGTGGGGA	GTGGCGAGCC	CTCAGATGCT	GCATATAAGC	AGCTGCTTTT

9020	9030	9040	9050	9060
TGCTGTACT	GGGTCTCTCT	GGTTAGACCA	GATTTGAGCC	TGGGAGCTCT
9070	9080	9090	9097	10
CTGGCTAACT	AGGGAACCCA	CTGCTTAAGC	CTCAATA	AAGCTTGCCT
20	30	40	50	60
TGAGTGCTTC	AAGTAGTGTG	TGCCCCGTCTG	TTGTGTGACT	CTGGTAACTA
70	80	90	100	110
GAGATCCCTC	AGACCCTTTT	AGTCAGTGTG	GAAAATCTCT	AGCAGTGGCG
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18. The purified recombinant DNA of claim 17, wherein said nucleic acid is labeled with a label selected from the group consisting of a radioisotope, an enzyme, a fluorescent label, and a chromophore label.

19. A method of using the purified recombinant DNA of claim 17 for detecting the presence of HIV-1 RNA comprising:

- (a) providing a cell-free supernatant of a biological fluid comprising cells infected with HIV-1;
- (b) disrupting HIV-1 virions in the cell-free supernatant to release HIV-1 RNA; and
- (c) detecting the presence of HIV-1 RNA by contacting the HIV-1 RNA with the purified recombinant DNA of claim 17 and detecting hybridization between the HIV-1 RNA and the purified recombinant DNA.

20. The method of claim 19, wherein the biological fluid is blood.

21. A method of using the purified recombinant DNA of claim 18 for detecting the presence of HIV-1 RNA comprising:

- (a) providing a cell-free supernatant of a biological fluid comprising cells infected with HIV-1;
- (b) disrupting HIV-1 virions in the cell-free supernatant to release HIV-1 RNA; and
- (c) detecting the presence of HIV-1 RNA by contacting the HIV-1 RNA with the purified recombinant DNA of claim 18 and detecting hybridization between the HIV-1 RNA and the purified recombinant DNA.

22. The method of claim 21, wherein the biological fluid is blood.

25. A method for detecting the presence of HIV-1 RNA comprising:

- (a) providing a cell-free supernatant of a biological fluid comprising cells infected with HIV-1;
- (b) disrupting HIV-1 virions in the cell-free supernatant to release HIV-1 RNA; and
- (c) detecting the presence of HIV-1 RNA.

27. The method of claim 25, wherein the presence of HIV-1 RNA is detected by contacting the HIV-1 RNA with the DNA of claim 17 and detecting hybridization between the HIV-1 RNA and the purified recombinant DNA.

28. The method of claim 25, wherein the presence of HIV-1 RNA is detected by contacting the HIV-1 RNA with the DNA of claim 18 and detecting hybridization between the HIV-1 RNA and the purified recombinant DNA.

29. A method for preparing HIV-1 RNA for detecting the presence of HIV-1 RNA comprising:

- (a) providing a cell-free supernatant of a biological fluid comprising cells infected with HIV-1;
- (b) disrupting HIV-1 virions in the cell-free supernatant to release HIV-1 RNA.

30. The method of claim 29, further comprising detecting the presence of HIV-1 RNA by contacting the HIV-1 RNA with the DNA of claim 17 and detecting hybridization between the HIV-1 RNA and the purified recombinant DNA.

31. The method of claim 29, further comprising detecting the presence of HIV-1 RNA by contacting the HIV-1 RNA with the DNA of claim 18 and detecting hybridization between the HIV-1 RNA and the purified recombinant DNA.

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- (a) providing a cell-free supernatant of a biological fluid comprising cells infected with HIV-1;

(b) isolating HIV-1 virions from the cell-free supernatant; and

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35. A purified fragment of the recombinant DNA of claim 17, wherein said fragment comprises the sequence:  
CTCAATAAAGCTTGCCTTG.

36. The purified fragment of claim 35, wherein said nucleic acid is labeled with a label selected from the group consisting of a radioisotope, an enzyme, a fluorescent label, and a chromophore label.

37. A method of using the purified fragment of claim 35 for detecting the presence of HIV-1 RNA comprising:

(a) providing a cell-free supernatant of a biological fluid comprising cells infected with HIV-1;

(b) disrupting HIV-1 virions in the cell-free supernatant to release HIV-1 RNA; and

(c) detecting the presence of HIV-1 RNA by contacting the HIV-1 RNA with the purified fragment of claim 35 and detecting hybridization between the HIV-1 RNA and the purified fragment.

38. The method of claim 37, wherein the biological fluid is blood.

39. A method of using the purified fragment of claim 36 for detecting the presence of HIV-1 RNA comprising:

(a) providing a cell-free supernatant of a biological fluid comprising cells infected with HIV-1;

(b) disrupting HIV-1 virions in the cell-free supernatant to release HIV-1 RNA; and

(c) detecting the presence of HIV-1 RNA by contacting the HIV-1 RNA with the purified fragment of claim 36 and detecting hybridization between the HIV-1 RNA and the purified fragment.

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PATENT  
Customer No. 22,852  
Attorney Docket No. 3495.0010-20

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TYPE 1 (HIV-1) )

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P.O. Box 1450  
Alexandria, VA 22313-1450

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**STATEMENT OF FRANÇOISE REY**  
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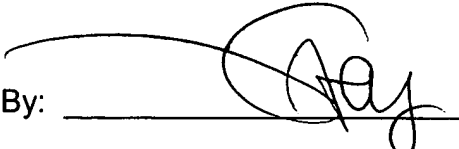
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By:  \_\_\_\_\_

Date: 23 mar 2006

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Inventors: Marc ALIZON et al.

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CACCAGGGCC	AGGGGTCAGA	TATCCACTGA	CCTTTGGATG	GTGCTACAAG
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CTAGTACCAG	TTGAGCCAGA	TAAGGTAGAA	GAGGCCAATA	AAGGAGAGAA
8770	8780	8790	8800	8810
CACCAGCTTG	TTACACCCTG	TGAGCCTGCA	TGGAATGGAT	GACCCTGAGA
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GAGAAGTGTT	AGAGTGGAGG	TTTGACAGCC	GCCTAGCATT	TCATCACGTG
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GCCCGAGAGC	TGCATCCGGA	GTA CTTCAAG	AACTGCTGAC	ATCGAGCTTG
8920	8930	8940	8950	8960
CTACAAGGGA	CTTTCCGCTG	GGGACTTTCC	AGGGAGGCGT	GGCCTGGGCG
8970	8980	8990	9000	9010
GAACTGGGGA	GTGGCGAGCC	CTCAGATGCT	GCATATAAGC	AGCTGCTTTT

9020	9030	9040	9050	9060
TGCCTGTACT	GGGTCTCTCT	GGTTAGACCA	GATTTGAGCC	TGGGAGCTCT
9070	9080	9090	9097	10
CTGGCTAACT	AGGGAACCCA	CTGCTTAAGC	CTCAATA	AAGCTTGCCT
20	30	40	50	60
TGAGTGCTTC	AAGTAGTGTG	TGCCCCGTCTG	TTGTGTGACT	CTGGTAACTA
70	80	90	100	110
GAGATCCCTC	AGACCCTTTT	AGTCAGTGTG	GAAAATCTCT	AGCAGTGGCG
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CCCGAACAGG	GACTTGAAAG	CGAAAGGGAA	ACCAGAGGAG	CTCTCTCGA

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19. A method of using the purified recombinant DNA of claim 17 for detecting the presence of HIV-1 RNA comprising:

- (a) providing a cell-free supernatant of a biological fluid comprising cells infected with HIV-1;
- (b) disrupting HIV-1 virions in the cell-free supernatant to release HIV-1 RNA; and
- (c) detecting the presence of HIV-1 RNA by contacting the HIV-1 RNA with the purified recombinant DNA of claim 17 and detecting hybridization between the HIV-1 RNA and the purified recombinant DNA.

20. The method of claim 19, wherein the biological fluid is blood.

21. A method of using the purified recombinant DNA of claim 18 for detecting the presence of HIV-1 RNA comprising:

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- (b) disrupting HIV-1 virions in the cell-free supernatant to release HIV-1 RNA; and
- (c) detecting the presence of HIV-1 RNA by contacting the HIV-1 RNA with the purified recombinant DNA of claim 18 and detecting hybridization between the HIV-1 RNA and the purified recombinant DNA.

22. The method of claim 21, wherein the biological fluid is blood.

25. A method for detecting the presence of HIV-1 RNA comprising:

- (a) providing a cell-free supernatant of a biological fluid comprising cells infected with HIV-1;
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- (c) detecting the presence of HIV-1 RNA.

27. The method of claim 25, wherein the presence of HIV-1 RNA is detected by contacting the HIV-1 RNA with the DNA of claim 17 and detecting hybridization between the HIV-1 RNA and the purified recombinant DNA.

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36. The purified fragment of claim 35, wherein said nucleic acid is labeled with a label selected from the group consisting of a radioisotope, an enzyme, a fluorescent label, and a chromophore label.

37. A method of using the purified fragment of claim 35 for detecting the presence of HIV-1 RNA comprising:

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(b) disrupting HIV-1 virions in the cell-free supernatant to release HIV-1 RNA; and

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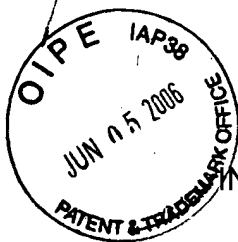
39. A method of using the purified fragment of claim 36 for detecting the presence of HIV-1 RNA comprising:

(a) providing a cell-free supernatant of a biological fluid comprising cells infected with HIV-1;

(b) disrupting HIV-1 virions in the cell-free supernatant to release HIV-1 RNA; and

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In re Application of: )  
 ) Group Art Unit: 1637  
Marc Alizon et al. )  
 ) Examiner: Jeffrey N. Fredman  
Application No.: 08/308,219 )  
 ) Confirmation No.: 4832  
Filed: September 19,1994 )  
 )  
For: DNA SEQUENCE OF THE LTR  
REGION OF HUMAN  
IMMUNODEFICIENCY VIRUS  
TYPE 1 (HIV-1)

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Sir:

**STATEMENT OF MARIE-THERESE NUGEYRE**  
**(Being Added As An Inventor)**

I have read U.S. application Serial No. 08/308,219.

I am informed that I was not named as an inventor in application Serial No.  
08/308,219 when the application was filed in the U.S. Patent and Trademark Office.

I have been informed that the claims in U.S. application Serial No. 08/308,219  
have been amended by adding claims 17-22, 25, and 27-40 to the application.

I am informed that a copy of claims 17-22, 25, and 27-40 is attached hereto.

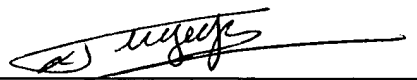
I have read claims 17-22, 25, and 27-40, which I am informed were added to  
U.S. application Serial No. 08/308,219 to claim previously unclaimed subject matter.

I understand that I am being added as an inventor to U.S. application Serial No. 08/308,219.

I have been informed that my addition as an inventor to U.S. application Serial No. 08/308,219 is necessitated by the amendment of the claims by adding claims 17-22, 25, and 27-40 to the application.

The inventorship error resulting from the amendment of the claims by adding claims 17-22, 25, and 27-40 to U.S. application Serial No. 08/308,219 occurred without deceptive intention on my part.

I hereby declare that all statements made of my own knowledge and belief are true and that all statements made on information and belief are believed to be true and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

By: 

Date: May 29 2006

U.S. Patent Application No. 08/308,219

Filed: September 19, 1994

Inventors: Marc ALIZON et al.

Div. of 07/158,652 (02/22/88);

Div. of 06/771,248 (08/30/85);

CIP of 07/999,410 (12/31/92);

Cont. of 07/499,210 (03/19/90);

Cont of 06/771,230 (08/30/85);

CIP of 06/706,562 (02/28/85)'

CIP of 06/558,109 (12/5/83)

DI No.: 84-37

Our Reference: 03495.0010-20000

Pending Claims

17. A purified recombinant DNA of human immunodeficiency virus type 1 (HIV-1), wherein the DNA comprises the sequence:

8570	8580	8590	8600	8610
GGGGGACTGG	AAGGGCTAAT	TCACTCCCAA	CGAAGACAAG	ATATCCTTGA
8620	8630	8640	8650	8660
TCTGTGGATC	TACCACACAC	AAGGCTACTT	CCCTGATTGG	CAGAACTACA
8670	8680	8690	8700	8710
CACCAGGGCC	AGGGGTCAGA	TATCCACTGA	CCTTTGGATG	GTGCTACAAG
8720	8730	8740	8750	8760
CTAGTACCAG	TTGAGCCAGA	TAAGGTAGAA	GAGGCCAATA	AAGGAGAGAA
8770	8780	8790	8800	8810
CACCAGCTTG	TTACACCCTG	TGAGCCTGCA	TGGAATGGAT	GACCCTGAGA
8820	8830	8840	8850	8860
GAGAAGTGTT	AGAGTGGAGG	TTTGACAGCC	GCCTAGCATT	TCATCACGTG
8870	8880	8890	8900	8910
GCCCGAGAGC	TGCATCCGGA	GTA CTTCAAG	AACTGCTGAC	ATCGAGCTTG
8920	8930	8940	8950	8960
CTACAAGGGA	CTTTCCGCTG	GGGACTTTCC	AGGGAGGCGT	GGCCTGGGCG
8970	8980	8990	9000	9010
GAACTGGGGA	GTGGCGAGCC	CTCAGATGCT	GCATATAAGC	AGCTGCTTTT

9020	9030	9040	9050	9060
TGCCTGTACT	GGGTCTCTCT	GGTTAGACCA	GATTTGAGCC	TGGGAGCTCT
9070	9080	9090	9097	10
CTGGCTAACT	AGGGAACCCA	CTGCTTAAGC	CTCAATA	AAGCTTGCCT
20	30	40	50	60
TGAGTGCTTC	AAGTAGTGTG	TGCCCCGTCTG	TTGTGTGACT	CTGGTAACTA
70	80	90	100	110
GAGATCCCTC	AGACCCTTTT	AGTCAGTGTG	GAAAATCTCT	AGCAGTGGCG
120	130	140	150	159
CCCGAACAGG	GACTTGAAAG	CGAAAGGGAA	ACCAGAGGAG	CTCTCTCGA

18. The purified recombinant DNA of claim 17, wherein said nucleic acid is labeled with a label selected from the group consisting of a radioisotope, an enzyme, a fluorescent label, and a chromophore label.

19. A method of using the purified recombinant DNA of claim 17 for detecting the presence of HIV-1 RNA comprising:

- (a) providing a cell-free supernatant of a biological fluid comprising cells infected with HIV-1;
- (b) disrupting HIV-1 virions in the cell-free supernatant to release HIV-1 RNA; and
- (c) detecting the presence of HIV-1 RNA by contacting the HIV-1 RNA with the purified recombinant DNA of claim 17 and detecting hybridization between the HIV-1 RNA and the purified recombinant DNA.

20. The method of claim 19, wherein the biological fluid is blood.

21. A method of using the purified recombinant DNA of claim 18 for detecting the presence of HIV-1 RNA comprising:

- (a) providing a cell-free supernatant of a biological fluid comprising cells infected with HIV-1;
- (b) disrupting HIV-1 virions in the cell-free supernatant to release HIV-1 RNA; and
- (c) detecting the presence of HIV-1 RNA by contacting the HIV-1 RNA with the purified recombinant DNA of claim 18 and detecting hybridization between the HIV-1 RNA and the purified recombinant DNA.

22. The method of claim 21, wherein the biological fluid is blood.

25. A method for detecting the presence of HIV-1 RNA comprising:

- (a) providing a cell-free supernatant of a biological fluid comprising cells infected with HIV-1;
- (b) disrupting HIV-1 virions in the cell-free supernatant to release HIV-1 RNA; and
- (c) detecting the presence of HIV-1 RNA.

27. The method of claim 25, wherein the presence of HIV-1 RNA is detected by contacting the HIV-1 RNA with the DNA of claim 17 and detecting hybridization between the HIV-1 RNA and the purified recombinant DNA.

28. The method of claim 25, wherein the presence of HIV-1 RNA is detected by contacting the HIV-1 RNA with the DNA of claim 18 and detecting hybridization between the HIV-1 RNA and the purified recombinant DNA.

29. A method for preparing HIV-1 RNA for detecting the presence of HIV-1 RNA comprising:

- (a) providing a cell-free supernatant of a biological fluid comprising cells infected with HIV-1;
- (b) disrupting HIV-1 virions in the cell-free supernatant to release HIV-1 RNA.

30. The method of claim 29, further comprising detecting the presence of HIV-1 RNA by contacting the HIV-1 RNA with the DNA of claim 17 and detecting hybridization between the HIV-1 RNA and the purified recombinant DNA.

31. The method of claim 29, further comprising detecting the presence of HIV-1 RNA by contacting the HIV-1 RNA with the DNA of claim 18 and detecting hybridization between the HIV-1 RNA and the purified recombinant DNA.

32. A method for preparing HIV-1 RNA for detecting the presence of HIV-1 RNA comprising:

- (a) providing a cell-free supernatant of a biological fluid comprising cells infected with HIV-1;

(b) isolating HIV-1 virions from the cell-free supernatant; and

(c) disrupting the virions to release HIV-1 RNA.

33. The method of claim 32, further comprising detecting the presence of HIV-1 RNA by contacting the HIV-1 RNA with the DNA of claim 17 and detecting hybridization between the HIV-1 RNA and the purified recombinant DNA.

34. The method of claim 32, further comprising detecting the presence of HIV-1 RNA by contacting the HIV-1 RNA with the DNA of claim 18 and detecting hybridization between the HIV-1 RNA and the purified recombinant DNA.

35. A purified fragment of the recombinant DNA of claim 17, wherein said fragment comprises the sequence:  
CTCAATAAAGCTTGCCTTG.

36. The purified fragment of claim 35, wherein said nucleic acid is labeled with a label selected from the group consisting of a radioisotope, an enzyme, a fluorescent label, and a chromophore label.

37. A method of using the purified fragment of claim 35 for detecting the presence of HIV-1 RNA comprising:

(a) providing a cell-free supernatant of a biological fluid comprising cells infected with HIV-1;

(b) disrupting HIV-1 virions in the cell-free supernatant to release HIV-1 RNA; and

(c) detecting the presence of HIV-1 RNA by contacting the HIV-1 RNA with the purified fragment of claim 35 and detecting hybridization between the HIV-1 RNA and the purified fragment.

38. The method of claim 37, wherein the biological fluid is blood.

39. A method of using the purified fragment of claim 36 for detecting the presence of HIV-1 RNA comprising:

(a) providing a cell-free supernatant of a biological fluid comprising cells infected with HIV-1;

(b) disrupting HIV-1 virions in the cell-free supernatant to release HIV-1 RNA; and

(c) detecting the presence of HIV-1 RNA by contacting the HIV-1 RNA with the purified fragment of claim 36 and detecting hybridization between the HIV-1 RNA and the purified fragment.

40. The method of claim 39, wherein the biological fluid is blood.



PATENT  
Customer No. 22,852  
Attorney Docket No. 3495.0010-20

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Marc Alizon et al.

Application No.: 08/308,219

Filed: September 19, 1994

For: DNA SEQUENCE OF THE LTR  
REGION OF HUMAN  
IMMUNODEFICIENCY VIRUS  
TYPE 1 (HIV-1)

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Sir:

**STATEMENT ON BEHALF OF JACQUELINE GRUEST**  
**(Being Added As An Inventor)**

I, JACQUES GRUEST, am the heir of the estate of JACQUELINE GRUEST, who is deceased.

I have been informed that Jacqueline Gruest was not named as an inventor in application Serial No. 08/308,219 when the application was filed in the U.S. Patent and Trademark Office.

I have been informed that the claims in U.S. application Serial No. 08/308,219 have been amended by adding claims 17-22, 25, and 27-40 to the application.

I have been informed that a copy of claims 17-22, 25, and 27-40 is attached hereto.

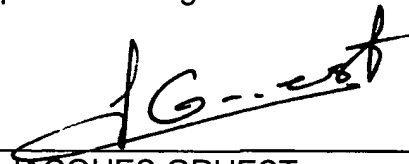
I have been informed that claims 17-22, 25, and 27-40 were added to U.S. application Serial No. 08/308,219 to claim previously unclaimed subject matter.

I have been informed that Jacqueline Gruet is being added as an inventor to U.S. application Serial No. 08/308,219.

I have been informed that the addition of Jacqueline Gruet as an inventor to U.S. application Serial No. 08/308,219 is necessitated by the amendment of the claims by adding claims 17-22, 25, and 27-40 to the application.

On information and belief, the inventorship error resulting from the amendment of the claims by adding claims 17-22, 25, and 27-40 to U.S. application Serial No. 08/308,219 occurred without deceptive intention on the part of Jacqueline Gruet.

I hereby declare that all statements made of my own knowledge and belief are true and that all statements made on information and belief are believed to be true and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

By:   
JACQUES GRUEST  
Heir of the Estate of Jacqueline Gruet

Date: 25.05.2006

U.S. Patent Application No. 08/308,219

Filed: September 19, 1994

Inventors: Marc ALIZON et al.

Div. of 07/158,652 (02/22/88);

Div. of 06/771,248 (08/30/85);

CIP of 07/999,410 (12/31/92);

Cont. of 07/499,210 (03/19/90);

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DI No.: 84-37

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8670	8680	8690	8700	8710
CACCAGGGCC	AGGGGTCAGA	TATCCACTGA	CCTTTGGATG	GTGCTACAAG
8720	8730	8740	8750	8760
CTAGTACCAG	TTGAGCCAGA	TAAGGTAGAA	GAGGCCAATA	AAGGAGAGAA
8770	8780	8790	8800	8810
CACCAGCTTG	TTACACCCTG	TGAGCCTGCA	TGGAATGGAT	GACCCTGAGA
8820	8830	8840	8850	8860
GAGAAGTGTT	AGAGTGGAGG	TTTGACAGCC	GCCTAGCATT	TCATCACGTG
8870	8880	8890	8900	8910
GCCCGAGAGC	TGCATCCGGA	GTA CTTCAAG	AACTGCTGAC	ATCGAGCTTG
8920	8930	8940	8950	8960
CTACAAGGGA	CTTTCCGCTG	GGGACTTTCC	AGGGAGGCGT	GGCCTGGGCG
8970	8980	8990	9000	9010
GAAGTGGGGA	GTGGCGAGCC	CTCAGATGCT	GCATATAAGC	AGCTGCTTTT

9020	9030	9040	9050	9060
TGCCTGTACT	GGGTCTCTCT	GGTTAGACCA	GATTTGAGCC	TGGGAGCTCT
9070	9080	9090	9097	10
CTGGCTAACT	AGGGAACCCA	CTGCTTAAGC	CTCAATA	AAGCTTGCCT
20	30	40	50	60
TGAGTGCTTC	AAGTAGTGTG	TGCCCCGTCTG	TTGTGTGACT	CTGGTAACTA
70	80	90	100	110
GAGATCCCTC	AGACCCTTTT	AGTCAGTGTG	GAAAATCTCT	AGCAGTGGCG
120	130	140	150	159
CCCGAACAGG	GACTTGAAAG	CGAAAGGGAA	ACCAGAGGAG	CTCTCTCGA

18. The purified recombinant DNA of claim 17, wherein said nucleic acid is labeled with a label selected from the group consisting of a radioisotope, an enzyme, a fluorescent label, and a chromophore label.

19. A method of using the purified recombinant DNA of claim 17 for detecting the presence of HIV-1 RNA comprising:

- (a) providing a cell-free supernatant of a biological fluid comprising cells infected with HIV-1;
- (b) disrupting HIV-1 virions in the cell-free supernatant to release HIV-1 RNA; and
- (c) detecting the presence of HIV-1 RNA by contacting the HIV-1 RNA with the purified recombinant DNA of claim 17 and detecting hybridization between the HIV-1 RNA and the purified recombinant DNA.

20. The method of claim 19, wherein the biological fluid is blood.

21. A method of using the purified recombinant DNA of claim 18 for detecting the presence of HIV-1 RNA comprising:

- (a) providing a cell-free supernatant of a biological fluid comprising cells infected with HIV-1;
- (b) disrupting HIV-1 virions in the cell-free supernatant to release HIV-1 RNA; and
- (c) detecting the presence of HIV-1 RNA by contacting the HIV-1 RNA with the purified recombinant DNA of claim 18 and detecting hybridization between the HIV-1 RNA and the purified recombinant DNA.

22. The method of claim 21, wherein the biological fluid is blood.

25. A method for detecting the presence of HIV-1 RNA comprising:

- (a) providing a cell-free supernatant of a biological fluid comprising cells infected with HIV-1;
- (b) disrupting HIV-1 virions in the cell-free supernatant to release HIV-1 RNA; and
- (c) detecting the presence of HIV-1 RNA.

27. The method of claim 25, wherein the presence of HIV-1 RNA is detected by contacting the HIV-1 RNA with the DNA of claim 17 and detecting hybridization between the HIV-1 RNA and the purified recombinant DNA.

28. The method of claim 25, wherein the presence of HIV-1 RNA is detected by contacting the HIV-1 RNA with the DNA of claim 18 and detecting hybridization between the HIV-1 RNA and the purified recombinant DNA.

29. A method for preparing HIV-1 RNA for detecting the presence of HIV-1 RNA comprising:

- (a) providing a cell-free supernatant of a biological fluid comprising cells infected with HIV-1;
- (b) disrupting HIV-1 virions in the cell-free supernatant to release HIV-1 RNA.

30. The method of claim 29, further comprising detecting the presence of HIV-1 RNA by contacting the HIV-1 RNA with the DNA of claim 17 and detecting hybridization between the HIV-1 RNA and the purified recombinant DNA.

31. The method of claim 29, further comprising detecting the presence of HIV-1 RNA by contacting the HIV-1 RNA with the DNA of claim 18 and detecting hybridization between the HIV-1 RNA and the purified recombinant DNA.

32. A method for preparing HIV-1 RNA for detecting the presence of HIV-1 RNA comprising:

- (a) providing a cell-free supernatant of a biological fluid comprising cells infected with HIV-1;

(b) isolating HIV-1 virions from the cell-free supernatant; and

(c) disrupting the virions to release HIV-1 RNA.

33. The method of claim 32, further comprising detecting the presence of HIV-1 RNA by contacting the HIV-1 RNA with the DNA of claim 17 and detecting hybridization between the HIV-1 RNA and the purified recombinant DNA.

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35. A purified fragment of the recombinant DNA of claim 17, wherein said fragment comprises the sequence:  
CTCAATAAAGCTTGCCTTG.

36. The purified fragment of claim 35, wherein said nucleic acid is labeled with a label selected from the group consisting of a radioisotope, an enzyme, a fluorescent label, and a chromophore label.

37. A method of using the purified fragment of claim 35 for detecting the presence of HIV-1 RNA comprising:

(a) providing a cell-free supernatant of a biological fluid comprising cells infected with HIV-1;

(b) disrupting HIV-1 virions in the cell-free supernatant to release HIV-1 RNA; and

(c) detecting the presence of HIV-1 RNA by contacting the HIV-1 RNA with the purified fragment of claim 35 and detecting hybridization between the HIV-1 RNA and the purified fragment.

38. The method of claim 37, wherein the biological fluid is blood.

39. A method of using the purified fragment of claim 36 for detecting the presence of HIV-1 RNA comprising:

(a) providing a cell-free supernatant of a biological fluid comprising cells infected with HIV-1;

(b) disrupting HIV-1 virions in the cell-free supernatant to release HIV-1 RNA; and

(c) detecting the presence of HIV-1 RNA by contacting the HIV-1 RNA with the purified fragment of claim 36 and detecting hybridization between the HIV-1 RNA and the purified fragment.

40. The method of claim 39, wherein the biological fluid is blood.



PATENT  
Customer No. 22,852  
Attorney Docket No. 3495.0010-20

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Marc Alizon et al.

Application No.: 08/308,219

Filed: September 19, 1994

For: DNA SEQUENCE OF THE LTR  
REGION OF HUMAN  
IMMUNODEFICIENCY VIRUS  
TYPE 1 (HIV-1)

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Sir:

**STATEMENT OF CHARLES DAUGUET**  
**(Being Added As An Inventor)**

I have read U.S. application Serial No. 08/308,219.

I am informed that I was not named as an inventor in application Serial No.  
08/308,219 when the application was filed in the U.S. Patent and Trademark Office.

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have been amended by adding claims 17-22, 25, and 27-40 to the application.

I am informed that a copy of claims 17-22, 25, and 27-40 is attached hereto.

I have read claims 17-22, 25, and 27-40, which I am informed were added to  
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The inventorship error resulting from the amendment of the claims by adding claims 17-22, 25, and 27-40 to U.S. application Serial No. 08/308,219 occurred without deceptive intention on my part.

I hereby declare that all statements made of my own knowledge and belief are true and that all statements made on information and belief are believed to be true and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

By: Charles D. Dargatzis

Date: 26 Mar 2006

U.S. Patent Application No. 08/308,219

Filed: September 19, 1994

Inventors: Marc ALIZON et al.

Div. of 07/158,652 (02/22/88);

Div. of 06/771,248 (08/30/85);

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8770	8780	8790	8800	8810
CACCAGCTTG	TTACACCCTG	TGAGCCTGCA	TGGAATGGAT	GACCCTGAGA
8820	8830	8840	8850	8860
GAGAAGTGTT	AGAGTGGAGG	TTTGACAGCC	GCCTAGCATT	TCATCACGTG
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8920	8930	8940	8950	8960
CTACAAGGGA	CTTTCCGCTG	GGGACTTTCC	AGGGAGGCGT	GGCCTGGGCG
8970	8980	8990	9000	9010
GAACTGGGGA	GTGGCGAGCC	CTCAGATGCT	GCATATAAGC	AGCTGCTTTT

9020	9030	9040	9050	9060
TGCCTGTACT	GGGTCTCTCT	GGTTAGACCA	GATTTGAGCC	TGGGAGCTCT
9070	9080	9090	9097	10
CTGGCTAACT	AGGGAACCCA	CTGCTTAAGC	CTCAATA	AAGCTTGCCT
20	30	40	50	60
TGAGTGCTTC	AAGTAGTGTG	TGCCCCGTCTG	TTGTGTGACT	CTGGTAACTA
70	80	90	100	110
GAGATCCCTC	AGACCCTTTT	AGTCAGTGTG	GAAAATCTCT	AGCAGTGGCG
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CCCGAACAGG	GACTTGAAAG	CGAAAGGGAA	ACCAGAGGAG	CTCTCTCGA

18. The purified recombinant DNA of claim 17, wherein said nucleic acid is labeled with a label selected from the group consisting of a radioisotope, an enzyme, a fluorescent label, and a chromophore label.

19. A method of using the purified recombinant DNA of claim 17 for detecting the presence of HIV-1 RNA comprising:

- (a) providing a cell-free supernatant of a biological fluid comprising cells infected with HIV-1;
- (b) disrupting HIV-1 virions in the cell-free supernatant to release HIV-1 RNA; and
- (c) detecting the presence of HIV-1 RNA by contacting the HIV-1 RNA with the purified recombinant DNA of claim 17 and detecting hybridization between the HIV-1 RNA and the purified recombinant DNA.

20. The method of claim 19, wherein the biological fluid is blood.

21. A method of using the purified recombinant DNA of claim 18 for detecting the presence of HIV-1 RNA comprising:

- (a) providing a cell-free supernatant of a biological fluid comprising cells infected with HIV-1;
- (b) disrupting HIV-1 virions in the cell-free supernatant to release HIV-1 RNA; and
- (c) detecting the presence of HIV-1 RNA by contacting the HIV-1 RNA with the purified recombinant DNA of claim 18 and detecting hybridization between the HIV-1 RNA and the purified recombinant DNA.

22. The method of claim 21, wherein the biological fluid is blood.

25. A method for detecting the presence of HIV-1 RNA comprising:

- (a) providing a cell-free supernatant of a biological fluid comprising cells infected with HIV-1;
- (b) disrupting HIV-1 virions in the cell-free supernatant to release HIV-1 RNA; and
- (c) detecting the presence of HIV-1 RNA.

27. The method of claim 25, wherein the presence of HIV-1 RNA is detected by contacting the HIV-1 RNA with the DNA of claim 17 and detecting hybridization between the HIV-1 RNA and the purified recombinant DNA.

28. The method of claim 25, wherein the presence of HIV-1 RNA is detected by contacting the HIV-1 RNA with the DNA of claim 18 and detecting hybridization between the HIV-1 RNA and the purified recombinant DNA.

29. A method for preparing HIV-1 RNA for detecting the presence of HIV-1 RNA comprising:

- (a) providing a cell-free supernatant of a biological fluid comprising cells infected with HIV-1;
- (b) disrupting HIV-1 virions in the cell-free supernatant to release HIV-1 RNA.

30. The method of claim 29, further comprising detecting the presence of HIV-1 RNA by contacting the HIV-1 RNA with the DNA of claim 17 and detecting hybridization between the HIV-1 RNA and the purified recombinant DNA.

31. The method of claim 29, further comprising detecting the presence of HIV-1 RNA by contacting the HIV-1 RNA with the DNA of claim 18 and detecting hybridization between the HIV-1 RNA and the purified recombinant DNA.

32. A method for preparing HIV-1 RNA for detecting the presence of HIV-1 RNA comprising:

- (a) providing a cell-free supernatant of a biological fluid comprising cells infected with HIV-1;

(b) isolating HIV-1 virions from the cell-free supernatant; and

(c) disrupting the virions to release HIV-1 RNA.

33. The method of claim 32, further comprising detecting the presence of HIV-1 RNA by contacting the HIV-1 RNA with the DNA of claim 17 and detecting hybridization between the HIV-1 RNA and the purified recombinant DNA.

34. The method of claim 32, further comprising detecting the presence of HIV-1 RNA by contacting the HIV-1 RNA with the DNA of claim 18 and detecting hybridization between the HIV-1 RNA and the purified recombinant DNA.

35. A purified fragment of the recombinant DNA of claim 17, wherein said fragment comprises the sequence:  
CTCAATAAAGCTTGCCTTG.

36. The purified fragment of claim 35, wherein said nucleic acid is labeled with a label selected from the group consisting of a radioisotope, an enzyme, a fluorescent label, and a chromophore label.

37. A method of using the purified fragment of claim 35 for detecting the presence of HIV-1 RNA comprising:

(a) providing a cell-free supernatant of a biological fluid comprising cells infected with HIV-1;

(b) disrupting HIV-1 virions in the cell-free supernatant to release HIV-1 RNA; and

(c) detecting the presence of HIV-1 RNA by contacting the HIV-1 RNA with the purified fragment of claim 35 and detecting hybridization between the HIV-1 RNA and the purified fragment.

38. The method of claim 37, wherein the biological fluid is blood.

39. A method of using the purified fragment of claim 36 for detecting the presence of HIV-1 RNA comprising:

(a) providing a cell-free supernatant of a biological fluid comprising cells infected with HIV-1;

(b) disrupting HIV-1 virions in the cell-free supernatant to release HIV-1 RNA; and

(c) detecting the presence of HIV-1 RNA by contacting the HIV-1 RNA with the purified fragment of claim 36 and detecting hybridization between the HIV-1 RNA and the purified fragment.

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In re Application of: )  
 ) Group Art Unit: 1637  
Marc Alizon et al. )  
 ) Examiner: Jeffrey N. Fredman  
Application No.: 08/308,219 )  
 ) Confirmation No.: 4832  
Filed: September 19,1994 )  
 )  
For: DNA SEQUENCE OF THE LTR  
REGION OF HUMAN  
IMMUNODEFICIENCY VIRUS  
TYPE 1 (HIV-1)

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Sir:

**STATEMENT OF WILLY ROZENBAUM**  
**(Being Added As An Inventor)**

I have read U.S. application Serial No. 08/308,219.

I am informed that I was not named as an inventor in application Serial No.  
08/308,219 when the application was filed in the U.S. Patent and Trademark Office.

I have been informed that the claims in U.S. application Serial No. 08/308,219  
have been amended by adding claims 17-22, 25, and 27-40 to the application.

I am informed that a copy of claims 17-22, 25, and 27-40 is attached hereto.

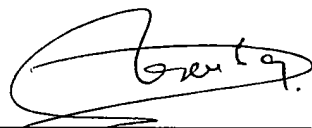
I have read claims 17-22, 25, and 27-40, which I am informed were added to  
U.S. application Serial No. 08/308,219 to claim previously unclaimed subject matter.

I understand that I am being added as an inventor to U.S. application Serial No. 08/308,219.

I have been informed that my addition as an inventor to U.S. application Serial No. 08/308,219 is necessitated by the amendment of the claims by adding claims 17-22, 25, and 27-40 to the application.

The inventorship error resulting from the amendment of the claims by adding claims 17-22, 25, and 27-40 to U.S. application Serial No. 08/308,219 occurred without deceptive intention on my part.

I hereby declare that all statements made of my own knowledge and belief are true and that all statements made on information and belief are believed to be true and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

By:   
Willy Rorenbaum.  
Date: 25 May 2006

U.S. Patent Application No. 08/308,219

Filed: September 19, 1994

Inventors: Marc ALIZON et al.

Div. of 07/158,652 (02/22/88);

Div. of 06/771,248 (08/30/85);

CIP of 07/999,410 (12/31/92);

Cont. of 07/499,210 (03/19/90);

Cont of 06/771,230 (08/30/85);

CIP of 06/706,562 (02/28/85)'

CIP of 06/558,109 (12/5/83)

DI No.: 84-37

Our Reference: 03495.0010-20000

Pending Claims

17. A purified recombinant DNA of human immunodeficiency virus type 1 (HIV-1), wherein the DNA comprises the sequence:

8570	8580	8590	8600	8610
GGGGGACTGG	AAGGGCTAAT	TCACTCCCAA	CGAAGACAAG	ATATCCTTGA
8620	8630	8640	8650	8660
TCTGTGGATC	TACCACACAC	AAGGCTACTT	CCCTGATTGG	CAGAACTACA
8670	8680	8690	8700	8710
CACCAGGGCC	AGGGGTCAGA	TATCCACTGA	CCTTTGGATG	GTGCTACAAG
8720	8730	8740	8750	8760
CTAGTACCAG	TTGAGCCAGA	TAAGGTAGAA	GAGGCCAATA	AAGGAGAGAA
8770	8780	8790	8800	8810
CACCAGCTTG	TTACACCCTG	TGAGCCTGCA	TGGAATGGAT	GACCCTGAGA
8820	8830	8840	8850	8860
GAGAAGTGTT	AGAGTGGAGG	TTTGACAGCC	GCCTAGCATT	TCATCACGTG
8870	8880	8890	8900	8910
GCCCGAGAGC	TGCATCCGGA	GTA CTTCAAG	AACTGCTGAC	ATCGAGCTTG
8920	8930	8940	8950	8960
CTACAAGGGA	CTTTCCGCTG	GGGACTTTCC	AGGGAGGCGT	GGCCTGGGCG
8970	8980	8990	9000	9010
GAAGTGGGGA	GTGGCGAGCC	CTCAGATGCT	GCATATAAGC	AGCTGCTTTT

9020	9030	9040	9050	9060
TGCCTGTACT	GGGTCTCTCT	GGTTAGACCA	GATTTGAGCC	TGGGAGCTCT
9070	9080	9090	9097	10
CTGGCTAACT	AGGGAACCCA	CTGCTTAAGC	CTCAATA	AAGCTTGCCT
20	30	40	50	60
TGAGTGCTTC	AAGTAGTGTG	TGCCCCGTCTG	TTGTGTGACT	CTGGTAACTA
70	80	90	100	110
GAGATCCCTC	AGACCCTTTT	AGTCAGTGTG	GAAAATCTCT	AGCAGTGGCG
120	130	140	150	159
CCCGAACAGG	GACTTGAAAG	CGAAAGGGAA	ACCAGAGGAG	CTCTCTCGA

18. The purified recombinant DNA of claim 17, wherein said nucleic acid is labeled with a label selected from the group consisting of a radioisotope, an enzyme, a fluorescent label, and a chromophore label.

19. A method of using the purified recombinant DNA of claim 17 for detecting the presence of HIV-1 RNA comprising:

- (a) providing a cell-free supernatant of a biological fluid comprising cells infected with HIV-1;
- (b) disrupting HIV-1 virions in the cell-free supernatant to release HIV-1 RNA; and
- (c) detecting the presence of HIV-1 RNA by contacting the HIV-1 RNA with the purified recombinant DNA of claim 17 and detecting hybridization between the HIV-1 RNA and the purified recombinant DNA.

20. The method of claim 19, wherein the biological fluid is blood.

21. A method of using the purified recombinant DNA of claim 18 for detecting the presence of HIV-1 RNA comprising:

- (a) providing a cell-free supernatant of a biological fluid comprising cells infected with HIV-1;
- (b) disrupting HIV-1 virions in the cell-free supernatant to release HIV-1 RNA; and
- (c) detecting the presence of HIV-1 RNA by contacting the HIV-1 RNA with the purified recombinant DNA of claim 18 and detecting hybridization between the HIV-1 RNA and the purified recombinant DNA.

22. The method of claim 21, wherein the biological fluid is blood.

25. A method for detecting the presence of HIV-1 RNA comprising:

- (a) providing a cell-free supernatant of a biological fluid comprising cells infected with HIV-1;
- (b) disrupting HIV-1 virions in the cell-free supernatant to release HIV-1 RNA; and
- (c) detecting the presence of HIV-1 RNA.

27. The method of claim 25, wherein the presence of HIV-1 RNA is detected by contacting the HIV-1 RNA with the DNA of claim 17 and detecting hybridization between the HIV-1 RNA and the purified recombinant DNA.

28. The method of claim 25, wherein the presence of HIV-1 RNA is detected by contacting the HIV-1 RNA with the DNA of claim 18 and detecting hybridization between the HIV-1 RNA and the purified recombinant DNA.

29. A method for preparing HIV-1 RNA for detecting the presence of

HIV-1 RNA comprising:

(a) providing a cell-free supernatant of a biological fluid comprising cells infected with HIV-1;

(b) disrupting HIV-1 virions in the cell-free supernatant to release HIV-1 RNA.

30. The method of claim 29, further comprising detecting the presence of HIV-1 RNA by contacting the HIV-1 RNA with the DNA of claim 17 and detecting hybridization between the HIV-1 RNA and the purified recombinant DNA.

31. The method of claim 29, further comprising detecting the presence of HIV-1 RNA by contacting the HIV-1 RNA with the DNA of claim 18 and detecting hybridization between the HIV-1 RNA and the purified recombinant DNA.

32. A method for preparing HIV-1 RNA for detecting the presence of

HIV-1 RNA comprising:

(a) providing a cell-free supernatant of a biological fluid comprising cells infected with HIV-1;

(b) isolating HIV-1 virions from the cell-free supernatant; and

(c) disrupting the virions to release HIV-1 RNA.

33. The method of claim 32, further comprising detecting the presence of HIV-1 RNA by contacting the HIV-1 RNA with the DNA of claim 17 and detecting hybridization between the HIV-1 RNA and the purified recombinant DNA.

34. The method of claim 32, further comprising detecting the presence of HIV-1 RNA by contacting the HIV-1 RNA with the DNA of claim 18 and detecting hybridization between the HIV-1 RNA and the purified recombinant DNA.

35. A purified fragment of the recombinant DNA of claim 17, wherein said fragment comprises the sequence:  
CTCAATAAAGCTTGCCTTG.

36. The purified fragment of claim 35, wherein said nucleic acid is labeled with a label selected from the group consisting of a radioisotope, an enzyme, a fluorescent label, and a chromophore label.

37. A method of using the purified fragment of claim 35 for detecting the presence of HIV-1 RNA comprising:

(a) providing a cell-free supernatant of a biological fluid comprising cells infected with HIV-1;

(b) disrupting HIV-1 virions in the cell-free supernatant to release HIV-1 RNA; and

(c) detecting the presence of HIV-1 RNA by contacting the HIV-1 RNA with the purified fragment of claim 35 and detecting hybridization between the HIV-1 RNA and the purified fragment.

38. The method of claim 37, wherein the biological fluid is blood.

39. A method of using the purified fragment of claim 36 for detecting the presence of HIV-1 RNA comprising:

(a) providing a cell-free supernatant of a biological fluid comprising cells infected with HIV-1;

(b) disrupting HIV-1 virions in the cell-free supernatant to release HIV-1 RNA; and

(c) detecting the presence of HIV-1 RNA by contacting the HIV-1 RNA with the purified fragment of claim 36 and detecting hybridization between the HIV-1 RNA and the purified fragment.

40. The method of claim 39, wherein the biological fluid is blood.



PATENT  
Customer No. 22,852  
Attorney Docket No. 3495.0010-20

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: )  
Marc Alizon et al. ) Group Art Unit: 1637  
Application No.: 08/308,219 ) Examiner: Jeffrey N. Fredman  
Filed: September 19, 1994 ) Confirmation No.: 4832  
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IMMUNODEFICIENCY VIRUS )  
TYPE 1 (HIV-1) )

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Sir:

**STATEMENT OF FRANÇOISE BRON-VEZINET**  
**(Being Added As An Inventor)**

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I am informed that I was not named as an inventor in application Serial No. 08/308,219 when the application was filed in the U.S. Patent and Trademark Office.

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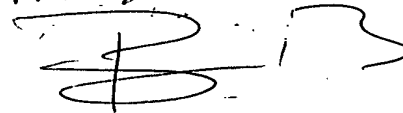
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By:

FRANÇOISE BRUN-JEANNE  


Date:

30/05/06

U.S. Patent Application No. 08/308,219

Filed: September 19, 1994

Inventors: Marc ALIZON et al.

Div. of 07/158,652 (02/22/88);

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8670	8680	8690	8700	8710
CACCAGGGCC	AGGGGTCAGA	TATCCACTGA	CCTTTGGATG	GTGCTACAAG
8720	8730	8740	8750	8760
CTAGTACCAG	TTGAGCCAGA	TAAGGTAGAA	GAGGCCAATA	AAGGAGAGAA
8770	8780	8790	8800	8810
CACCAGCTTG	TTACACCCTG	TGAGCCTGCA	TGGAATGGAT	GACCCTGAGA
8820	8830	8840	8850	8860
GAGAAGTGTT	AGAGTGGAGG	TTTGACAGCC	GCCTAGCATT	TCATCACGTG
8870	8880	8890	8900	8910
GCCCCGAGAGC	TGCATCCGGA	GTACTTCAAG	AACTGCTGAC	ATCGAGCTTG
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CTACAAGGGA	CTTTCCGCTG	GGGACTTTCC	AGGGAGGCGT	GGCCTGGGCG
8970	8980	8990	9000	9010
GAACTGGGGA	GTGGCGAGCC	CTCAGATGCT	GCATATAAGC	AGCTGCTTTT

9020	9030	9040	9050	9060
TGCCTGTACT	GGGTCTCTCT	GGTTAGACCA	GATTTGAGCC	TGGGAGCTCT
9070	9080	9090	9097	10
CTGGCTAACT	AGGGAACCCA	CTGCTTAAGC	CTCAATA	AAGCTTGCCT
20	30	40	50	60
TGAGTGCTTC	AAGTAGTGTG	TGCCCCGTCTG	TTGTGTGACT	CTGGTAACTA
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19. A method of using the purified recombinant DNA of claim 17 for detecting the presence of HIV-1 RNA comprising:

- (a) providing a cell-free supernatant of a biological fluid comprising cells infected with HIV-1;
- (b) disrupting HIV-1 virions in the cell-free supernatant to release HIV-1 RNA; and
- (c) detecting the presence of HIV-1 RNA by contacting the HIV-1 RNA with the purified recombinant DNA of claim 17 and detecting hybridization between the HIV-1 RNA and the purified recombinant DNA.

20. The method of claim 19, wherein the biological fluid is blood.

28. The method of claim 25, wherein the presence of HIV-1 RNA is detected by contacting the HIV-1 RNA with the DNA of claim 18 and detecting hybridization between the HIV-1 RNA and the purified recombinant DNA.

29. A method for preparing HIV-1 RNA for detecting the presence of HIV-1 RNA comprising:

- (a) providing a cell-free supernatant of a biological fluid comprising cells infected with HIV-1;
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32. A method for preparing HIV-1 RNA for detecting the presence of HIV-1 RNA comprising:

- (a) providing a cell-free supernatant of a biological fluid comprising cells infected with HIV-1;

21. A method of using the purified recombinant DNA of claim 18 for detecting the presence of HIV-1 RNA comprising:

(a) providing a cell-free supernatant of a biological fluid comprising cells infected with HIV-1;

(b) disrupting HIV-1 virions in the cell-free supernatant to release HIV-1 RNA; and

(c) detecting the presence of HIV-1 RNA by contacting the HIV-1 RNA with the purified recombinant DNA of claim 18 and detecting hybridization between the HIV-1 RNA and the purified recombinant DNA.

22. The method of claim 21, wherein the biological fluid is blood.

25. A method for detecting the presence of HIV-1 RNA comprising:

(a) providing a cell-free supernatant of a biological fluid comprising cells infected with HIV-1;

(b) disrupting HIV-1 virions in the cell-free supernatant to release HIV-1 RNA; and

(c) detecting the presence of HIV-1 RNA.

27. The method of claim 25, wherein the presence of HIV-1 RNA is detected by contacting the HIV-1 RNA with the DNA of claim 17 and detecting hybridization between the HIV-1 RNA and the purified recombinant DNA.

(b) isolating HIV-1 virions from the cell-free supernatant; and

(c) disrupting the virions to release HIV-1 RNA.

33. The method of claim 32, further comprising detecting the presence of HIV-1 RNA by contacting the HIV-1 RNA with the DNA of claim 17 and detecting hybridization between the HIV-1 RNA and the purified recombinant DNA.

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36. The purified fragment of claim 35, wherein said nucleic acid is labeled with a label selected from the group consisting of a radioisotope, an enzyme, a fluorescent label, and a chromophore label.

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(a) providing a cell-free supernatant of a biological fluid comprising cells infected with HIV-1;

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39. A method of using the purified fragment of claim 36 for detecting the presence of HIV-1 RNA comprising:

(a) providing a cell-free supernatant of a biological fluid comprising cells infected with HIV-1;

(b) disrupting HIV-1 virions in the cell-free supernatant to release HIV-1 RNA; and

(c) detecting the presence of HIV-1 RNA by contacting the HIV-1 RNA with the purified fragment of claim 36 and detecting hybridization between the HIV-1 RNA and the purified fragment.

40. The method of claim 39, wherein the biological fluid is blood.



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Re Application of:

Marc Alizon et al.

Application No.: 08/308,219

Filed: September 19, 1994

For: DNA SEQUENCE OF THE LTR  
REGION OF HUMAN  
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TYPE 1 (HIV-1)

)  
) Group Art Unit: 1637  
)  
) Examiner: Jeffrey N. Fredman  
)  
) Confirmation No.: 4832  
)  
)

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Sir:

**SUBMISSION UNDER 37 C.F.R. § 3.73(b)**

Institut Pasteur, duly organized under the laws of France and having its principal place of business at 28, rue du Docteur Roux, 75724 Paris Cedex 15, France, submits that it, together with the United States of America as represented by the Secretary of the Department of Health and Human Services, are the Assignees and owners of 100% of the right, title, and interest in the patent application identified above. Institut Pasteur's ownership interest is evidenced by:

An Assignment from the inventors to Institut Pasteur and Centre Nationale de la Recherche Scientifique, jointly, which was recorded in the Patent and Trademark Office at Reel 016769, Frame 0280, on July 14, 2005; copies of the recorded Assignment and the Notice of Recordation are attached hereto as Exhibit A; and

An Assignment from Centre Nationale de la Recherche Scientifique, having its principal place of business at 3, Rue Michel-Ange, 75794 Paris, Cedex 16, France, to Institut Pasteur, a copy of which is attached hereto as Exhibit B; and

Assignments from Solange Chamaret, Claudine Axler-Blin, Françoise Rey, Marie Therese Nugeyre, Jacqueline Gruet, Charles Dauguet, Willy Rozenbaum, Christine Rouzioux, Françoise Brun-Vezinet, Luc Montagnier, Jean-Claude Chermann, Françoise Barre-Sinoussi, and Pierre Tiollais, who are being added as inventors to the patent application identified above, to Institut Pasteur; copies of these Assignments are included in Exhibit C attached hereto.

The undersigned is authorized to act on behalf of the assignee, Institut Pasteur.

I hereby declare that all statements made of my own knowledge and belief are true and that all statements made on information and belief are believed to be true and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Respectfully submitted,

*A. Dautry*

By: \_\_\_\_\_  
Name: Alice Dautry  
Title: President  
Assignee: Institut Pasteur

Dated: \_\_\_\_\_

*June 1<sup>st</sup>, 2006*

7.1425

To the Director of the U.S. Patent and Trademark Office Please record the attached original		U.S. Department of Commerce Patent and Trademark Office Atty. Docket No. 3485.0010-15 Attorney Customer Number: 22,85- Mail Stop Assignment Recordation Services	
1. Name of conveying party(ies): 1. Marc ALIZON 2. Pierre SONIGO 3. Cole STEWART 4. Oliver DANOS 5. Simon WAIN-HOBSON		2. Name and address of receiving party(ies): 1. Institut Pasteur 25-28, rue du Doctor Roux 75724 Paris Cedex 15, France 2. Centre Nationale de la Recherche Scientifique 15, Quai Anatole France 75007 Paris, France	
Additional name(s) of conveying party(ies) attached? <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No			
3. Nature of conveyance: <input checked="" type="checkbox"/> Assignment <input type="checkbox"/> Merger <input type="checkbox"/> Security Agreement <input type="checkbox"/> Change of Name <input type="checkbox"/> Other: [Describe]			
Execution Date: February 7, 1986		Additional name(s) & Address(es) attached? <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	
4. Application number(s) or patent number(s): If this document is being filed together with a new application, the execution date of the application: A. Patent Application Number(s): 1. Appin. No. 06/771,248 (08/30/1985) Additional numbers attached? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No		B. Patent Number(s): 1. US No. 5,980,900 (11/09/1999)	
5. Name and address of party to whom correspondence concerning document should be mailed: Name: Salvatore J. Arrigo, Reg. No. 48,063 Internal Address: FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P. Street Address: 901 New York Avenue, N.W. City: Washington, D.C. State: Zip: 20001-4413		6. Total number of applications and registrations involved: 14 7. Total fee (37 CFR 1.21(h) and 3.41): \$560 (\$40 x 14) <input checked="" type="checkbox"/> Enclosed (Please charge deficiency to deposit account 06-0916) <input type="checkbox"/> Authorized to be charged to deposit account 8. Deposit Account No.: 06-0916	
9. Statement and signature To the best of my knowledge and belief, the foregoing information is true and correct and any attached copy is a true copy of the original document. 07/18/2005 18:00 00000140 5980900 01 FC 8021 560.00 DP Salvatore J. Arrigo Signature: <i>[Signature]</i> Date: 7/14/05 Total number of pages including cover sheet, attachments and documents: 3			

01/21/05

PATENT  
REEL: 016769 FRAME: 0280

4. Application/Patent Numbers (Continued)

Patent Applications

2. Appln. No. 07/158,652 (02/22/1998)
3. Appln. No. 08/026,736 (03/04/1993)
4. Appln. No. 08/051,226 (04/23/1993)
5. Appln. No. 08/156,930 (11/24/1993)
6. Appln. No. 08/308,218 (09/19/1994)
7. Appln. No. 08/308,219 (09/19/1994)
8. Appln. No. 08/475,822 (06/07/1995)

Issued Patents

2. US No. 5,705,612 (01/06/1998)
3. US No. 6,894,152 (02/25/1994)
4. US No. 6,555,112 (04/29/2003)
5. US No. 6,261,564 (07/17/2001)
6. US No. 6,706,268 (03/16/2004)

**ASSIGNMENT  
FOR UNFILED APPLICATION FOR UNITED STATES PATENT  
(Sole or Joint Inventors)**

ALL NAMES AND  
OFFICE ADDRESSES  
(Inventors)  
(including country)

**WHEREAS:**

- ALIZON Marc, 71, rue du Cardinal Lemoine 75005 PARIS (France)
- SONIGO Pierre 23, rue Gutenberg 75015 PARIS (France)
- STEWART Cole  
48is Villa Denise 92320 CHATILLON (France)
- DANOS Oliver 1, Place Rollet 75015 PARIS (France)
- WAIN-HOBSON Simon 3, rue Jean de la Fontaine  
78180 MONTIGNY LES BRETONNEUX (France)

FILE OF  
VENTION

(hereinafter referred to as ASSIGNOR), have invented and own a certain invention entitled:

**CLONED DNA SEQUENCES RELATED TO THE GENOMIC RNA OF  
LYMPHADENOPATHY-ASSOCIATED VIRUS(LAV) AND... RNA**

for which application for Letters Patent of the United States has been executed on ~~XXXXXX~~  
~~XXXXXX~~, August 30, 1985,

ALL NAME AND  
ADDRESS (including  
country) of  
SIGNEE

**INSTITUT PASTEUR  
25-28, rue du Dr. Roux  
75724 PARIS CEDEX 15 (France) and**

**CENTRE NATIONAL DE LA RECHERCHE SCIENTIFIQUE  
15, Quai Anatole France  
75007 PARIS (France)**

(hereinafter referred to as ASSIGNEE), is desirous of acquiring the entire interest in, to and under said invention and the United States Letters Patent to be obtained therefor;

NOW, THEREFORE, TO ALL WHOM IT MAY CONCERN: Be it known that in consideration of the payment by ASSIGNEE to ASSIGNOR of the sum of One Dollar (\$1.00), the receipt of which is hereby acknowledged, and for other good and valuable consideration, ASSIGNOR hereby sells, assigns and transfers to ASSIGNEE the full and exclusive right, title and interest to said invention and all Letters Patent of the United States to be obtained therefor on said application or any continuation, division, renewal, substitute or reissue thereof for the full term or terms for which the same may be granted.

ASSIGNOR hereby covenants that no assignment, sale, agreement or encumbrance has been or will be made or entered into which would conflict with this assignment and sale;

ASSIGNOR further covenants that ASSIGNEE will, upon its request, be provided promptly with all pertinent facts and documents relating to said application, said invention and said Letters Patent as may be known and accessible to ASSIGNOR and will testify as to the same in any interference or litigation relating thereto and will promptly execute and deliver to ASSIGNEE or its legal representative any and all papers, instruments or affidavits required to apply for, obtain, maintain and enforce said application, said invention and said Letters Patent which may be necessary or desirable to carry out the purposes hereof.

IN WITNESS WHEREOF, We have hereunto set hand and seal this 7-2-1986  
(Date of Signing)

THE SIGNING  
is made by the person  
the date of signing  
the declaration and  
one of the parties or  
sign application.

INITIALS (S)  
- signatories must  
respond with the  
initials of the  
contract above.

*Stewart Cole*

*Pierre SONIGO*

*Marc ALIZON*

*Simon WAIN-HOBSON*

*Marc ALIZON*

*Simon WAIN-HOBSON*

NOTE: No witnessing, notarization or legalization is necessary, but can be included if desired as a crime.

RECORDED: 07/14/2005

PATENT  
REEL: 016769 FRAME: 0282

**ASSIGNMENT**

WHEREAS, by virtue of an Assignment recorded in the United States Patent and Trademark Office on Reel 016769, Frames 0280-282, on July 14, 2005, Centre Nationale de la Recherche Scientifique (hereinafter referred to as ASSIGNOR), is the owner of rights, title, and interest in United States Patent Application Serial No. 08/308,219, filed September 19, 1994, (Attorney Docket No. 3495.0010-20), in the name of Marc Allzon, Pierre Sonigo, Cole Stewart, Oliver Danos, and Simon Wain-Hobson and entitled DNA SEQUENCE OF THE LTR REGION OF HUMAN IMMUNODEFICIENCY VIRUS TYPE 1 (HIV-1).

WHEREAS, Institut Pasteur (hereinafter referred to as ASSIGNEE), is desirous of acquiring from ASSIGNOR the ASSIGNOR's rights, title, and interest in, to and under the aforesaid patent application and the invention therein in the United States of America and its territories and possessions.

NOW THEREFORE, in consideration of good and valuable consideration, receipt of which from ASSIGNEE is acknowledged by ASSIGNOR, ASSIGNOR hereby sells, assigns, and transfers to the ASSIGNEE, its lawful successors and assigns, all of ASSIGNOR's rights to said invention in the United States, its territories and possessions, and all of ASSIGNOR's rights, title, and interest in and to said United States patent application Serial No. 08/308,219, filed September 19, 1994, and in and to any Letters Patent, which may be granted therefor in the United States, its territories and possessions, and in and to reissues, reexaminations, and extensions thereof.

5,352-127

ASSIGNOR hereby authorizes and requests the Commissioner of Patents and Trademarks of the United States to issue any and all of said Letters Patent, when granted, to said ASSIGNEE, its lawful successors and assigns as the assignee of the entire right, title, and interest in and to the same, for the sole use and enjoyment of said ASSIGNEE, its lawful successors and assigns.

Furthermore, ASSIGNOR agrees that it will communicate to said ASSIGNEE, or its representatives, any facts known to ASSIGNOR respecting said invention, and, at ASSIGNEE's expense, testify in any legal proceedings, sign all lawful papers, execute all reissue, reexamination and extension applications, execute all necessary assignment papers to cause any and all of said Letters Patent to be issued to said ASSIGNEE, its lawful successors and assigns, to obtain and enforce proper protection for said invention in the United States, its territories and possessions.

IN WITNESS WHEREOF, ASSIGNOR has hereunto set its hand this 31<sup>st</sup> day of May, 2006.

Centre Nationale de la Recherche  
Scientifique

By: \_\_\_\_\_

Title: \_\_\_\_\_

**Marc J. LEDOUX**

*Chargé de  
Mission.*

Responsable du Pilotage  
de la Valorisation

TITLE: \_\_\_\_\_

**Frédéric FOUBERT**



JOINT INVENTION  
Attorney Docket No. 03495.0010-20

### ASSIGNMENT

WHEREAS I, the below named inventor, [hereinafter referred to as Assignor], have made an invention entitled:

**DNA SEQUENCE OF THE LTR REGION OF HUMAN  
IMMUNODEFICIENCY VIRUS TYPE 1 (HIV-1)**

for which an application for United States Letters Patent was filed on September 19, 1994 (Application No. 08/308,219); and

WHEREAS, Institut Pasteur, whose post office address is 28, rue du Docteur Roux, 75724 Paris Cedex 15, France (hereinafter referred to as Assignee), is desirous of securing the entire right, title, and interest in and to this invention in the United States, and in and to the application for United States Letters Patent on this invention and the Letters Patent to be issued upon this application;

NOW THEREFORE, be it known that for good and valuable consideration the receipt of which from Assignee is hereby acknowledged, I, as Assignor, have sold, assigned, transferred, and set over, and do hereby sell, assign, transfer, and set over unto the Assignee, its lawful successors and assigns, my entire right, title, and interest in and to this invention, and this application, and all divisions, and continuations thereof, and all Letters Patent of the United States, which may be granted thereon, and all reissues thereof, and I hereby authorize and request the Commissioner of Patents and Trademarks of the United States, whose duty it is to issue patents on applications as described above, to issue all Letters Patent for this invention to Assignee, its successors and assigns, in accordance with the terms of this Assignment;

AND, I HEREBY covenant that I have the full right to convey the interest assigned by this Assignment, and I have not executed and will not execute any agreement in conflict with this Assignment;

AND, I HEREBY further covenant and agree that I will, without further consideration, communicate with Assignee, its successors and assigns, any facts known to me respecting this invention, and testify in any legal proceeding, sign all lawful papers when called upon to do so, execute and deliver any and all papers that may be necessary or desirable to perfect the title to this invention in said Assignee, its successors or assigns, execute all divisional, continuation, and reissue applications, make all rightful oaths and generally do everything possible to aid Assignee, its successors and assigns, to obtain and enforce proper patent protection for this invention in the United States and any foreign country, it being understood that any expense incident to the execution of such papers shall be borne by the Assignee, its successors and assigns.

IN TESTIMONY WHEREOF, I have hereunto set my hand.

  
\_\_\_\_\_  
Solange Chamaret

24-05-06  
Date

JOINT INVENTION  
Attorney Docket No. 03495.0010-20

### ASSIGNMENT

WHEREAS I, the below named inventor, [hereinafter referred to as Assignor], have made an invention entitled:

**DNA SEQUENCE OF THE LTR REGION OF HUMAN  
IMMUNODEFICIENCY VIRUS TYPE 1 (HIV-1)**

for which an application for United States Letters Patent was filed on September 19, 1994 (Application No. 08/308,219); and

WHEREAS, Institut Pasteur, whose post office address is 28, rue du Docteur Roux, 75724 Paris Cedex 15, France (hereinafter referred to as Assignee), is desirous of securing the entire right, title, and interest in and to this invention in the United States, and in and to the application for United States Letters Patent on this invention and the Letters Patent to be issued upon this application;

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IN TESTIMONY WHEREOF, I have hereunto set my hand.

C-Axler-Blin  
Claudine Axler-Blin

26 Mar 2006  
Date

JOINT INVENTION  
Attorney Docket No. 03495.0010-20

### ASSIGNMENT

WHEREAS I, the below named inventor, [hereinafter referred to as Assignor], have made an invention entitled:

**DNA SEQUENCE OF THE LTR REGION OF HUMAN  
IMMUNODEFICIENCY VIRUS TYPE 1 (HIV-1)**

for which an application for United States Letters Patent was filed on September 19, 1994 (Application No. 08/308,219); and

WHEREAS, Institut Pasteur, whose post office address is 28, rue du Docteur Roux, 75724 Paris Cedex 15, France (hereinafter referred to as Assignee), is desirous of securing the entire right, title, and interest in and to this invention in the United States, and in and to the application for United States Letters Patent on this invention and the Letters Patent to be issued upon this application;

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IN TESTIMONY WHEREOF, I have hereunto set my hand.

  
\_\_\_\_\_  
Françoise Rey

  
\_\_\_\_\_  
Date

JOINT INVENTION  
Attorney Docket No. 03495.0010-20

### ASSIGNMENT

WHEREAS I, the below named inventor, [hereinafter referred to as Assignor], have made an invention entitled:

**DNA SEQUENCE OF THE LTR REGION OF HUMAN  
IMMUNODEFICIENCY VIRUS TYPE 1 (HIV-1)**

for which an application for United States Letters Patent was filed on September 19, 1994 (Application No. 08/308,219); and

WHEREAS, Institut Pasteur, whose post office address is 28, rue du Docteur Roux, 75724 Paris Cedex 15, France (hereinafter referred to as Assignee), is desirous of securing the entire right, title, and interest in and to this invention in the United States, and in and to the application for United States Letters Patent on this invention and the Letters Patent to be issued upon this application;

NOW THEREFORE, be it known that for good and valuable consideration the receipt of which from Assignee is hereby acknowledged, I, as Assignor, have sold, assigned, transferred, and set over, and do hereby sell, assign, transfer, and set over unto the Assignee, its lawful successors and assigns, my entire right, title, and interest in and to this invention, and this application, and all divisions, and continuations thereof, and all Letters Patent of the United States, which may be granted thereon, and all reissues thereof, and I hereby authorize and request the Commissioner of Patents and Trademarks of the United States, whose duty it is to issue patents on applications as described above, to issue all Letters Patent for this invention to Assignee, its successors and assigns, in accordance with the terms of this Assignment;

AND, I HEREBY covenant that I have the full right to convey the interest assigned by this Assignment, and I have not executed and will not execute any agreement in conflict with this Assignment;

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IN TESTIMONY WHEREOF, I have hereunto set my hand.

  
\_\_\_\_\_  
Marie-Therese Nugeyre

*May 29 2006*  
\_\_\_\_\_  
Date

JOINT INVENTION  
Attorney Docket No. 03495.0010-20

### ASSIGNMENT

WHEREAS, JACQUELINE GRUEST, [hereinafter referred to as Assignor], made an invention entitled:

**DNA SEQUENCE OF THE LTR REGION OF HUMAN  
IMMUNODEFICIENCY VIRUS TYPE 1 (HIV-1)**

for which an application for United States Letters Patent was filed on September 19, 1994 (Application No. 08/308,219); and

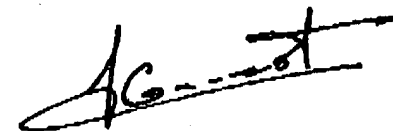
WHEREAS, Institut Pasteur, whose post office address is 28, rue du Docteur Roux, 75724 Paris Cedex 15, France (hereinafter referred to as Assignee), is desirous of securing the entire right, title, and interest in and to this invention in the United States, and in and to the application for United States Letters Patent on this invention and the Letters Patent to be issued upon this application;

NOW THEREFORE, be it known that for good and valuable consideration the receipt of which from Assignee is hereby acknowledged, I, as Assignor, have sold, assigned, transferred, and set over, and do hereby sell, assign, transfer, and set over unto the Assignee, its lawful successors and assigns, my entire right, title, and interest in and to this invention, and this application, and all divisions, and continuations thereof, and all Letters Patent of the United States, which may be granted thereon, and all reissues thereof, and I hereby authorize and request the Commissioner of Patents and Trademarks of the United States, whose duty it is to issue patents on applications as described above, to issue all Letters Patent for this invention to Assignee, its successors and assigns, in accordance with the terms of this Assignment;

AND, I HEREBY covenant that I have the full right to convey the interest assigned by this Assignment, and I have not executed and will not execute any agreement in conflict with this Assignment;

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IN TESTIMONY WHEREOF, I have hereunto set my hand.



Jacqueline Gruest

By: Jacques Gruest, Heir to the Estate of  
Jacqueline Gruest, Deceased

25.05.2006

Date

JOINT INVENTION  
Attorney Docket No. 03495.0010-20

### ASSIGNMENT

WHEREAS I, the below named inventor, [hereinafter referred to as Assignor], have made an invention entitled:

**DNA SEQUENCE OF THE LTR REGION OF HUMAN  
IMMUNODEFICIENCY VIRUS TYPE 1 (HIV-1)**

for which an application for United States Letters Patent was filed on September 19, 1994 (Application No. 08/308,219); and


WHEREAS, Institut Pasteur, whose post office address is 28, rue du Docteur Roux, 75724 Paris Cedex 15, France (hereinafter referred to as Assignee), is desirous of securing the entire right, title, and interest in and to this invention in the United States, and in and to the application for United States Letters Patent on this invention and the Letters Patent to be issued upon this application;

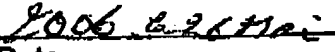
NOW THEREFORE, be it known that for good and valuable consideration the receipt of which from Assignee is hereby acknowledged, I, as Assignor, have sold, assigned, transferred, and set over, and do hereby sell, assign, transfer, and set over unto the Assignee, its lawful successors and assigns, my entire right, title, and interest in and to this invention, and this application, and all divisions, and continuations thereof, and all Letters Patent of the United States, which may be granted thereon, and all reissues thereof, and I hereby authorize and request the Commissioner of Patents and Trademarks of the United States, whose duty it is to issue patents on applications as described above, to issue all Letters Patent for this invention to Assignee, its successors and assigns, in accordance with the terms of this Assignment;

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IN TESTIMONY WHEREOF, I have hereunto set my hand.

  
Charles Dauguet

  
Date

JOINT INVENTION  
Attorney Docket No. 03495.0010-20

### ASSIGNMENT

WHEREAS I, the below named inventor, [hereinafter referred to as Assignor], have made an invention entitled:

**DNA SEQUENCE OF THE LTR REGION OF HUMAN  
IMMUNODEFICIENCY VIRUS TYPE 1 (HIV-1)**

for which an application for United States Letters Patent was filed on September 19, 1994 (Application No. 08/308,219); and

WHEREAS, Institut Pasteur, whose post office address is 28, rue du Docteur Roux, 75724 Paris Cedex 15, France (hereinafter referred to as Assignee), is desirous of securing the entire right, title, and interest in and to this invention in the United States, and in and to the application for United States Letters Patent on this invention and the Letters Patent to be issued upon this application;

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IN TESTIMONY WHEREOF, I have hereunto set my hand.



Willy Rozenbaum

25 May 2006  
Date

JOINT INVENTION  
Attorney Docket No. 03495.0010-20

### ASSIGNMENT

WHEREAS I, the below named inventor, [hereinafter referred to as Assignor], have made an invention entitled:

**DNA SEQUENCE OF THE LTR REGION OF HUMAN  
IMMUNODEFICIENCY VIRUS TYPE 1 (HIV-1)**

for which an application for United States Letters Patent was filed on September 19, 1994 (Application No. 08/308,219); and

WHEREAS, Institut Pasteur, whose post office address is 28, rue du Docteur Roux, 75724 Paris Cedex 15, France (hereinafter referred to as Assignee), is desirous of securing the entire right, title, and interest in and to this invention in the United States, and in and to the application for United States Letters Patent on this invention and the Letters Patent to be issued upon this application;

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IN TESTIMONY WHEREOF, I have hereunto set my hand.

Christine Rouzioux

30 05 2006  
Date

JOINT INVENTION  
Attorney Docket No. 03495.0010-20

### ASSIGNMENT

WHEREAS I, the below named Inventor, [hereinafter referred to as Assignor], have made an invention entitled:

#### DNA SEQUENCE OF THE LTR REGION OF HUMAN IMMUNODEFICIENCY VIRUS TYPE 1 (HIV-1)

for which an application for United States Letters Patent was filed on September 19, 1994 (Application No. 08/308,219); and

WHEREAS, Institut Pasteur, whose post office address is 28, rue du Docteur Roux, 75724 Paris Cedex 15, France (hereinafter referred to as Assignee), is desirous of securing the entire right, title, and interest in and to this invention in the United States, and in and to the application for United States Letters Patent on this invention and the Letters Patent to be issued upon this application;

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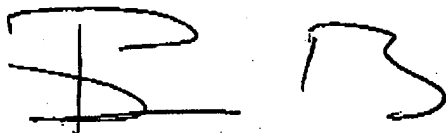
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IN TESTIMONY WHEREOF, I have hereunto set my hand.

FRANÇOIS BRUN-VEZINET  
François Brun-Vezinet

30/05/06  
Date



JOINT INVENTION  
Attorney Docket No. 03495.0010-20

### ASSIGNMENT

WHEREAS I, the below named inventor, [hereinafter referred to as Assignor], have made an invention entitled:

**DNA SEQUENCE OF THE LTR REGION OF HUMAN  
IMMUNODEFICIENCY VIRUS TYPE 1 (HIV-1)**

for which an application for United States Letters Patent was filed on September 19, 1994 (Application No. 08/308,219); and

WHEREAS, Institut Pasteur, whose post office address is 28, rue du Docteur Roux, 75724 Paris Cedex 15, France (hereinafter referred to as Assignee), is desirous of securing the entire right, title, and interest in and to this invention in the United States, and in and to the application for United States Letters Patent on this invention and the Letters Patent to be issued upon this application;

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IN TESTIMONY WHEREOF, I have hereunto set my hand.

  
\_\_\_\_\_  
Luc Montagnier

May 24 2006  
Date

JOINT INVENTION  
Attorney Docket No. 03495.0010-20

### ASSIGNMENT

WHEREAS I, the below named inventor, [hereinafter referred to as Assignor], have made an invention entitled:

**DNA SEQUENCE OF THE LTR REGION OF HUMAN  
IMMUNODEFICIENCY VIRUS TYPE 1 (HIV-1)**

for which an application for United States Letters Patent was filed on September 19, 1994 (Application No. 08/308,219); and

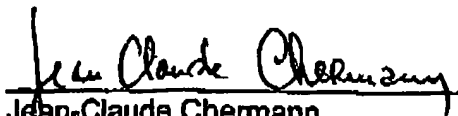
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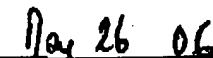
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IN TESTIMONY WHEREOF, I have hereunto set my hand.

  
\_\_\_\_\_  
Jean-Claude Chermann

  
\_\_\_\_\_  
Date

JOINT INVENTION  
Attorney Docket No. 03495.0010-20

### ASSIGNMENT

WHEREAS I, the below named inventor, [hereinafter referred to as Assignor], have made an invention entitled:

**DNA SEQUENCE OF THE LTR REGION OF HUMAN  
IMMUNODEFICIENCY VIRUS TYPE 1 (HIV-1)**

for which an application for United States Letters Patent was filed on September 19, 1994 (Application No. 08/308,219); and


WHEREAS, Institut Pasteur, whose post office address is 28, rue du Docteur Roux, 75724 Paris Cedex 15, France (hereinafter referred to as Assignee), is desirous of securing the entire right, title, and interest in and to this invention in the United States, and in and to the application for United States Letters Patent on this invention and the Letters Patent to be issued upon this application;

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IN TESTIMONY WHEREOF, I have hereunto set my hand.

  
\_\_\_\_\_  
Françoise Barre-Sinoussi

05.24.2006  
Date

JOINT INVENTION  
Attorney Docket No. 03495.0010-20

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IN TESTIMONY WHEREOF, I have hereunto set my hand.

  
\_\_\_\_\_  
Pierre Tiollais

24 mai 06  
Date

PATENT  
Customer No. 22,852  
Attorney Docket No. 3495.0010-20

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: )  
 ) Group Art Unit: 1637  
Marc Alizon et al. )  
 ) Examiner: Jeffrey N. Fredman  
Application No.: 08/308,219 )  
 ) Confirmation No.: 4832  
Filed: September 19, 1994 )  
 )  
For: DNA SEQUENCE OF THE LTR  
REGION OF HUMAN  
IMMUNODEFICIENCY VIRUS  
TYPE 1 (HIV-1)

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Sir:

**SUBMISSION UNDER 37 C.F.R. § 3.73(b)**

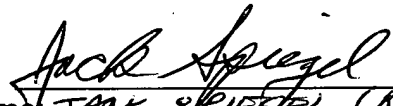
The United States of America as represented by the Secretary of the Department of Health and Human Services, having its principal place of business at 900 Rockville Pike, Bethesda, Maryland 20892, submits that it, together with Institut Pasteur of Paris, France, are the Assignees and owners of 100% of the right, title, and interest in the patent application identified above. The United States of America as represented by the Secretary of the Department of Health and Human Services' ownership interest is evidenced by:

Assignments from Robert C. Gallo, Mikulas Popovic, and Mangalasseril G. Sarngadharan, who are being added as inventors to the patent application identified above; copies of these Assignments are included in Exhibit A attached hereto.

The undersigned is authorized to act on behalf of the assignee, The United States of America as represented by the Secretary of the Department of Health and Human Services.

I hereby declare that all statements made of my own knowledge and belief are true and that all statements made on information and belief are believed to be true and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Respectfully submitted,

By:   
Name: JACK SPIEGEL (REG# 34,477)  
Title: SENIOR ADVISOR FOR TECHNOLOGY TRANSFER OPERATIONS  
Assignee: The United States of America  
as represented by the  
Secretary of the Department of  
Health and Human Services.

Dated: JUNE 5, 2006

1111556

### ASSIGNMENT

WHEREAS I, the below named inventor, [hereinafter referred to as Assignor], have made an invention entitled:

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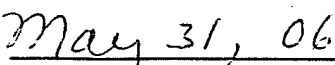
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IN TESTIMONY WHEREOF, I have hereunto set my hand.

  
Robert C. Gallo

  
Date

### ASSIGNMENT

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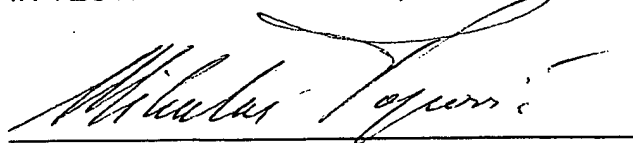
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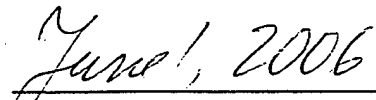
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IN TESTIMONY WHEREOF, I have hereunto set my hand.



Mikulas Popovic

  
Date

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IN TESTIMONY WHEREOF, I have hereunto set my hand.

*Mangalasseril G. Sarngadharan*

Mangalasseril G. Sarngadharan

*June 4, 2006*

Date



300-101-  
90-102-  
480-103-  
104-

Cloned DNA sequences related to the genomic RNA of lymphadenopathy-associated-virus (LAV) and proteins encoded by said LAV genomic RNA

5 The invention relates to cloned DNA sequences indistinguishable from genomic RNA and DNA of lymphadenopathy-associated virus (LAV), a process for their preparation and their uses. It relates more particularly to stable probes including a DNA sequence which can be used for the detection of the LAV virus or related viruses  
10 or DNA proviruses in any medium, particularly biological samples containing any of them. The invention also relates to polypeptides, whether glycosylated or not, encoded by said DNA sequences.

15 Lymphadenopathy-associated virus (LAV) is a human retrovirus first isolated from the lymph node of a homosexual patient with lymphadenopathy syndrome, frequently a prodrome or a benign form of acquired immune deficiency syndrome (AIDS). Subsequently other LAV isolates have been recovered from patients with AIDS or pre-AIDS. All available  
20 data are consistent with the virus being the causative agent of AIDS.

A method for cloning such DNA sequences has already been disclosed in British Patent Application Nr. 84 23659 filed on September 19, 1984. Reference is hereafter made to that application as concerns subject matter  
25 in common with the further improvements to the invention disclosed herein.

The present invention aims at providing additional new means which should not only also be useful for the  
30 detection of LAV or related viruses (hereafter more generally referred to as "LAV viruses"), but also have more versatility, particularly in detecting specific parts of the genomic DNA of said viruses whose expression products are not always directly detectable by immunological  
35 methods.

The present invention further aims at providing		
09/05/85 771248	2.101	300.00 CK
07/05/85 771248	2.102	90.00 CK
09/05/85 771248	2.103	40.00 CK
09/05/85 771248	2.104	100.00 CK

polypeptides containing sequences in common with polypeptides encoded by the LAV genomic RNA. It relates even more particularly to polypeptides comprising antigenic determinants included in the proteins encoded and expressed by the LAV genome occurring in nature. An additional object of the invention is to further provide means for the detection of proteins related to LAV virus, particularly for the diagnosis of AIDS or pre-AIDS or, to the contrary, for the detection of antibodies against the LAV virus or proteins related therewith, particularly in patients afflicted with AIDS or pre-AIDS or more generally in asymptomatic carriers and in blood-related products. Finally the invention also aims at providing immunogenic polypeptides, and more particularly protective polypeptides for use in the preparation of vaccine compositions against AIDS or related syndroms.

The present invention relates to additional DNA fragments, hybridizable with the genomic RNA of LAV as they will be disclosed hereafter, as well as with additional cDNA variants corresponding to the whole genomes of LAV viruses. It further relates to DNA recombinants containing said DNAs or cDNA fragments.

The invention relates more particularly to a cDNA variant corresponding to the whole of LAV retroviral genomes, which is characterized by a series of restriction sites in the order hereafter (from the 5' end to the 3' end).

The coordinates of the successive sites of the whole LAV genome (restriction map) are indicated hereafter too, with respect to the Hind III site (selected as of coordinate 1) which is located in the R region. The coordinates are estimated with an accuracy of  $\pm 200$  bp :

	Hind III	0
	Sac I	50
35	Hind III	520
	Pst I	800
	Hind III	1 100

	Bgl II	1 500
	Kpn I	3 500
	Kpn I	3 900
	Eco RI	4 100
5	Eco RI	5 300
	Sal I	5 500
	Kpn I	6 100
	Bgl II	6 500
	Bgl II	7 800
10	Hind III	7 850
	Bam HI	8 150
	Xho I	8 600
	Kpn I	8 700
	Bgl II	8 750
15	Bgl II	9 150
	Sac I	9 200
	Hind III	9 250

Another DNA variant according to this invention optionally contains an additional Hind III approximately at the 5 550 coordinate.

Reference is further made to fig. 1 which shows a more detailed restriction map of said whole-DNA (AJ19).

An even more detailed nucleotide sequence of a preferred DNA according to the invention is shown in fig. 4-12 hereafter.

The invention further relates to other preferred DNA fragments which will be referred to hereafter.

Additional features of the invention will appear in the course of the non-limitative disclosure of additional features of preferred DNAs of the invention, as well as of preferred polypeptides according to the invention. Reference will further be had to the drawings in which :

- fig. 1 is the restriction map of a complete LAV genome (clone AJ19) ;

- figs. 2 and 3 show diagrammatically parts of the three

possible reading phases of LAV genomic RNA, including the open reading frames (ORF) apparent in each of said reading phases :

- figs. 4-12 show the successive nucleotidic sequences of a complete LAV genome. The possible peptide sequences in relation to the three possible reading phases related to the nucleotide sequences shown are also indicated ;
- figs. 13-18 reiterate the sequence of part of the LAV genome containing the genes coding for the envelope proteins, with particular boxed peptidic sequences which corresponds to groups which normally carry glycosyl groups.

The sequencing and determination of sites of particular interest was carried out on a phage recombinant corresponding to AJ19 disclosed in the abovesaid British Patent application Nr. 84 23659. A method for preparing it is disclosed in that application.

The whole recombinant phage DNA of clone AJ19 (disclosed in the earlier application) was sonicated according to the protocol of DEININGER (1983), Analytical Biochem. 129, 216. the DNA was repaired by a Klenow reaction for 12 hours at 16°C. The DNA was electrophoresed through 0.8 % agarose gel and DNA in the size range of 300-600 bp was cut out and electroeluted and precipitated. Resuspended DNA (in 10 mM Tris, pH 8 ; 0.1 mM EDTA) was ligated into M13mp8 RF DNA (cut by the restriction enzyme SmaI and subsequently alkaline phosphated), using T4 DNA- and RNA-ligases (Maniatis T et al (1982) - Molecular cloning - Cold Spring Harbor Laboratory). An E. coli strain designated as TGI was used for further study. This strain has the following genotype :

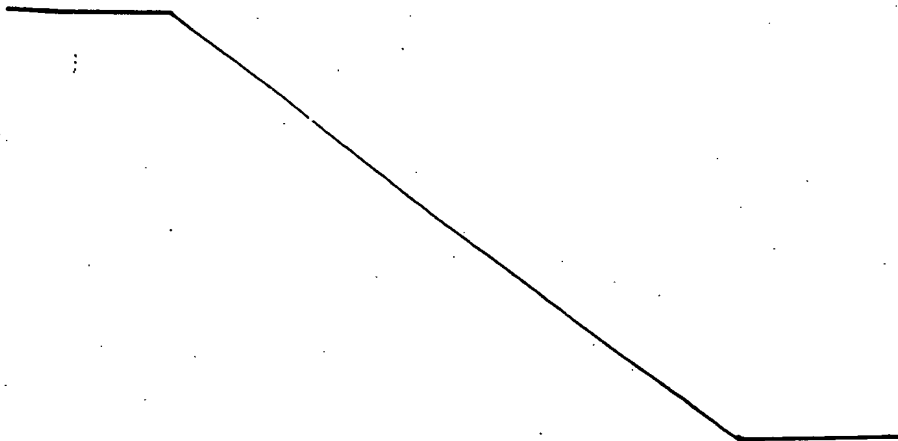
$\Delta lac$  pro, supE, thi.F' traD36, proAB, lacI<sup>q</sup>, ZAM15, r<sup>-</sup>

This E. coli TGI strain has the peculiarity of enabling recombinants to be recognized easily. The blue colour of the cells transfected with plasmids which did

not recombine with a fragment of LAV DNA is not modified. To the contrary cells transfected by a recombinant plasmid containing a LAV DNA fragment yield white colonies. The technique which was used is disclosed in Gene (1983), 28, 101.

This strain was transformed with the ligation mix using the Manahan method (Manahan D (1983) J. Mol. Biol. 166, 557). Cells were plated out on tryptone-agarose plate with IPTG and X-gal in soft agarose. White plaques were either picked and screened or screened directly in situ using nitrocellulose filters. Their DNAs were hybridized with nick-translated DNA inserts of pUC18 Hind III subclones of  $\lambda$ J19. this permitted the isolation of the plasmids or subclones of  $\lambda$  which are identified in the table hereafter. In relation to this table it should also be noted that the designation of each plasmid is followed by the deposition number of a cell culture of E. coli TGI containing the corresponding plasmid at the "Collection Nationale des Cultures de Micro-organismes" (C.N.C.M.) of the Pasteur Institute in Paris, France. A non-transformed TGI cell line was also deposited at the C.N.C.M. under Nr. I-364. All these deposits took place on November 15, 1984. The sizes of the corresponding inserts derived from the LAV genome have also been indicated.

25



TABLE

Essential features of the recombinant plasmids

5	- pJ19 - 1 plasmid	(I-365)	0.5 kb
	Hind III - Sac I - Hind III		
10	- pJ19 - 17 plasmid	(I-367)	0.6 kb
	Hind III - Pst I - Hind III		
	- pJ19 - 6 plasmid	(I-366)	1.5 kb
15	Hind III (5')		
	Bam HI		
	Xho I		
	Kpn I		
	Bgl II		
20	Sac I (3')		
	Hind III		
	- pJ19-13 plasmid	(I-368)	6.7 kb
25	Hind III (5')		
	Bgl II		
	Kpn I		
	Kpn I		
	Eco RI		
30	Eco RI		
	Sal I		
	Kpn I		
	Bgl II		
	Bgl II		
35	Hind III (3')		

Positively hybridizing M13 phage plates were grown up for 5 hours and the single-stranded DNAs were extracted.

M13mp8 subclones of  $\lambda$ J19 DNAs were sequenced according to the dideoxy method and technology devised by Sanger et al (Sanger et al (1977), Proc. Natl. Acad. Sci. USA, 74, 5463 and M13 cloning and sequencing handbook, AMERSHAM (1983). the 17-mer oligonucleotide primer  $\alpha$ -<sup>35</sup>SdATP (400Ci/mmol, AMERSHAM), and 0.5X-5X buffer gradient gels (Biggen M.O. et al (1983, Proc. Natl. Acad. Sci. USA, 50, 3963) were used. Gels were read and put into the computer under the programs of Staden (Staden R. (1982), Nucl. Acids Res. 10, 4731). All the appropriate references and methods can be found in the AMERSHAM M13 cloning and sequencing handbook.

The complete sequence of  $\lambda$ J19 was deduced from the experiments as further disclosed hereafter.

Figs. 4-12 provide the DNA nucleotide sequence of the complete genome of LAV. The numbering of the nucleotides starts from a left most Hind III restriction site (5'AAG...) of the restriction map. The numbering occurs in tens whereby the last zero number of each of the numbers occurring on the drawings is located just below the nucleotide corresponding to the nucleotides designated. I.e. the nucleotide at position 10 is T, the nucleotide at position 20 is C, etc..

Above each of the lines of the successive nucleotide sequences there are provided three lines of single letters corresponding to the amino acid sequence deduced from the DNA sequence (using the genetic code) for each at the three reading phases, whereby said single letters have the following meanings.

A : alanine  
R : arginine  
K : lysine  
H : histidine  
C : cysteine

M : méthionine  
 W : tryptophan  
 F : phenylalanine  
 Y : tyrosine  
 5 L : leucine  
 V : valine  
 I : isoleucine  
 G : glycine  
 T : thréonine  
 10 S : serine  
 E : glutamic acid  
 D : Aspartic acid  
 N : asparagine  
 Q : glutamine  
 15 P : proline.

The asterik signs "\*" correspond to stop codons (i.e. TAA, TAG and TGA).

20 Starting above the first line of the DNA nucleotidic sequence of fig. 4 the three reading phases are respectively marked "1", "2", "3", on the left handside of the drawing. The same relative presentation of the three theoritical reading phases is then used all over the successives lines of the LAV nucleotidic sequence.

25 Figs. 2 and 3 provide a diagrammatized representation of the lengths of the successive open reading frames corresponding to the successive reading phases (also referred to by numbers "1", "2" and "3" appearing in the left handside part of fig. 2). The relative positions of these open reading frames (ORF) with respect to the
 30 nucleotidic structure of the LAV genome is referred to by the scale of numbers representative of the respective positions of the corresponding nucleotides in the DNA sequence. The vertical bars correspond to the positions of the corresponding stop codons.

35 1) The "gag gene" (or ORF-gag)

The "gag gene" codes for core proteins.

Particularly it appears that a genomic fragment (ORF-gag) thought to code for the core antigens including the p25, p18 and p13 proteins is located between nucleotidic position 238 (starting with 5' CTA GCG GAG 3') and nucleotidic position 1759 (ending by CTCG TCA CAA 3'). The structure of the peptides or proteins encoded by parts of said ORF is deemed to be that corresponding to phase 2.

The methionine aminoacid "M" coded by the ATG at position 260-262 is the probable initiation methionine of the gag protein precursor. The end of ORF-gag and accordingly of gag protein appears to be located at position 1759.

The beginning of p25 protein, thought to start by a P-I-V-Q-N-I-Q-G-Q-M-V-M .... aminoacid sequence is thought to be coded for by the nucleotidic sequence CCTATA.... starting at position 656.

Hydrophilic peptides in the gag open reading frame are identified hereafter. They are defined starting from aminoacid 1 = Met (M) coded by the ATG starting from 260-2 in the LAV DNA sequence.

	Those hydrophilic peptides are
	12-32 aminoacids inclusive
	37-46        -        -
	49-79        -        -
25	88-153      -        -
	158-165     -        -
	178-188     -        -
	200-220     -        -
	226-234     -        -
30	239-264     -        -
	288-331     -        -
	352-361     -        -
	377-390     -        -
	399-432     -        -
35	437-484     -        -
	492-498     -        -

The invention also relates to any combination of these peptides.

2) The "pol gene" (or ORF-pol)

Figs. 4-12 also show that the DNA fragments  
 5 extending from nucleotidic position 1555 (starting with  
 5' TTT TTT .... 3' to nucleotidic position 5086 is thought  
 to correspond to the pol gene. The polypeptidic structure  
 of the corresponding polypeptides is deemed to be that  
 corresponding to phase 1. It stops at position 4563 (end  
 10 by 5' G GAT GAG GAT 3').

These genes are thought to code for the virus  
 polymerase or reverse transcriptase.

3) The envelope gene (or ORF-env)

The DNA sequence thought to code for envelope  
 15 proteins is thought to extend from nucleotidic position  
 5670 (starting with 5' AAA GAG GAG A.... 3') up to nucleo-  
 tidic position 8132 (ending by .... A ACT AAA GAA 3').  
 Polypeptidic structures of sequences of the envelope  
 protein correspond to those read according to the "phase  
 20 3" reading phase.

The start of env transcription is thought to be at  
 the level of the ATG codon at positions 5691-5693.

Additional feature of the envelope protein coded  
 by the env genes appear on figs. 13-18. These are to be  
 25 considered as paired figs. 13 and 14 ; 15 and 16 ; 17 and  
 18 respectively.

It is to be mentioned that because of format  
 difficulties.

Fig. 14 overlaps to some extent with fig. 13.

30 Fig. 16 overlaps to some extent with fig. 15.

Fig. 18 overlaps to some extent with fig. 17.

Thus for instance figs. 13 and 14 must be con-  
 sidered together. Particularly the sequence shown on the  
 first line on the top of fig. 13 overlaps with the  
 35 sequence shown on the first line on the top of fig. 14. In  
 other words the starting of the reading of the successive

sequences of the env gene as represented in figs. 13-18 involves first reading the first line at the top of fig. 13 then proceeding further with the first line of fig. 14. One then returns to the beginning of the second line of fig. 13, then again further proceed with the reading of the second line of page 14, etc... The same observations then apply to the reading of the paired figs. 15 and 16, and paired figs. 17 and 18, respectively.

The locations of neutralizing epitopes are further apparent in figs. 13-18. reference is more particularly made to the boxed groups of three letters included in the aminoacid sequences of the envelope proteins (reading phase 3) which can be designated generally by the formula N-X-S or N-X-T, wherein X is any other possible aminoacid. Thus the initial protein product of the env gene in a glycoprotein of molecular weight in excess of 91,000. These groups are deemed to generally carry glycosylated groups. These N-X-S and N-X-T groups with attached glycosylated groups form together hydrophylic regions of the protein and are deemed to be located at the periphery of and to be exposed outwardly with respect to the normal conformation of the proteins. Consequently they are considered as being epitopes which can efficiently be brought into play in vaccine compositions.

The invention thus concerns with more particularly peptide sequences included in the env-proteins and excizable therefrom (or having the same aminoacid structure), having sizes not exceeding 200 aminoacids.

Preferred peptides of this invention (referred to hereafter as a, b, c, d, e, f) are deemed to correspond to those encoded by the nucleotide sequences which extend respectively between the following positions :

- a) from about 6095 to about 6200
- b) " " 6260 " " 6310
- 35 c) " " 6390 " " 6440
- d) " " 6485 " " 6620

e) - " 6860 " " 6930  
 f) - " 7535 " " 7630

Other hydrophilic peptides in the env open reading frame are identified hereafter. they are defined starting  
 5 from

aminoacid 1 = lysine (K) coded by the AAA at position 5670-2 in the LAV DNA sequence.

These hydrophilic peptides are

8-23 aminoacids inclusive

10	63-78	"	"
	82-90	"	"
	97-123	"	"
	127-183	"	"
	197-201	"	"
15	239-294	"	"
	300-327	"	"
	334-381	"	"
	397-424	"	"
	466-500	"	"
20	510-523	"	"
	551-577	"	"
	594-603	"	"
	621-630	"	"
	657-679	"	"
25	719-758	"	"
	780-803	"	"

The invention also relates to any combination of these peptides.

#### 4) The other ORF

30 The invention further concerns DNA sequences which provide open reading frames defined as ORF-Q, ORF-R and as "1", "2", "3", "4", "5", the relative position of which appears more particularly in figs. 2 and 3.

These ORFs have the following locations :

35	ORF-Q	phase 1	start 4478	stop 5086
	ORF-R	" 2	" 8249	" 8896

ORF-1	"	1	"	5029	"	5316
ORF-2	"	2	"	5273	"	5515
ORF-3	"	1	"	5383	"	5616
ORF-4	"	2	"	5519	"	5773
5 ORF-5	"	1	"	7966	"	8279

The LTR (long terminal repeats) can be defined as lying between position 8560 and position 160 (end extending over position 9097/1). As a matter of fact the end of the genome is at 9097 and, because of the LTR structure of the retrovirus, links up with the beginning of the sequence :

Hind III  
CTCAATAAAGCTTGCCTTG

9097 1

The invention concerns more particularly all the DNA fragments which have been more specifically referred to hereabove and which correspond to open reading frames. It will be understood that the man skilled in the art will be able to obtain them all, for instance by cleaving an entire DNA corresponding to the complete genome of a LAV species, such as by cleavage by a partial or complete digestion thereof with a suitable restriction enzyme and by the subsequent recovery of the relevant fragments. The different DNAs disclosed in the earlier mentioned British Application can be resorted to also as a source of suitable fragments. The techniques disclosed hereabove for the isolation of the fragments which were then included in the plasmids referred to hereabove and which were then used for the DNA sequencing can be used.

Of course other methods can be used. Some of them have been exemplified in the earlier British Application. reference is for instance made to the following methods.

a) DNA can be transfected into mammalian cells with appropriate selection markers by a variety of techniques, calcium phosphate precipitation, polyethylene

glycol, protoplast-fusion, etc..

b) DNA fragments corresponding to genes can be cloned into expression vectors for E. coli, yeast- or mammalian cells and the resultant proteins purified.

5 c) The proviral DNA can be "shot-gunned" (fragmented) into procaryotic expression vectors to generate fusion polypeptides. Recombinant producing antigenically competent fusion proteins can be identified by simply screening the recombinants with antibodies against LAV  
10 antigens.

The invention also relates more specifically to cloned probes which can be made starting from any DNA fragment according to this invention, thus to recombinant DNAs containing such fragments, particularly any plasmids  
15 amplifiable in procaryotic or eucaryotic cells and carrying said fragments.

Using the cloned DNA fragments as a molecular hybridization probe - either by marking with radionucleotides or with fluorescent reagents - LAV virion RNA may be  
20 detected directly in the blood, body fluids and blood products (e.g. of the antihemophylic factors such as Factor VIII concentrates) and vaccines, i.e. hepatitis B vaccine. It has already been shown that whole virus can be detected in culture supernatants of LAV producing cells. A  
25 suitable method for achieving that detection comprises immobilizing virus onto said a support e.g. nitrocellulose filters, etc., disrupting the virion and hybridizing with labelled (radiolabelled or "cold" fluorescent- or enzyme-labelled) probes. Such an approach has already been  
30 developed for Hepatitis B virus in peripheral blood (according to SCOTTO J. et al. Hepatology (1983), 3, 379-384).

Probes according to the invention can also be used for rapid screening of genomic DNA derived from the tissue  
35 of patients with LAV related symptoms, to see if the proviral DNA or RNA is present in host tissue and other

tissues.

A method which can be used for such screening comprise the following steps : extraction of DNA from tissue, restriction enzyme cleavage of said DNA, electrophoresis of the fragments and Southern blotting of genomic DNA from tissues, subsequent hybridization with labelled cloned LAV proviral DNA. Hybridization in situ can also be used.

Lymphatic fluids and tissues and other non-lymphatic tissues of humans, primates and other mammalian species can also be screened to see if other evolutionary related retrovirus exist. The methods referred to hereabove can be used, although hybridization and washings would be done under non stringent conditions.

The DNA according to the invention can be used also for achieving the expression of LAV viral antigens for diagnostic purposes.

The invention also relates to the polypeptides themselves which can be expressed by the different DNAs of the inventions, particularly by the ORFs or fragments thereof, in appropriate hosts, particularly procaryotic or eucaryotic hosts, after transformation thereof with a suitable vector previously modified by the corresponding DNAs.

These polypeptides can be used as diagnostic tools, particularly for the detection of antibodies in biological media, particularly in sera or tissues of persons afflicted with pre-AIDS or AIDS, or simply carrying antibodies in the absence of any apparent disorders. Conversely the different peptides according to this invention can be used themselves for the production of antibodies, preferably monoclonal antibodies specific of the different peptides respectively. For the production of hybridomas secreting said monoclonal antibodies conventional production and screening methods are used. These monoclonal antibodies, which themselves are part of

the invention than provide very useful tools for the identification and even determination of relative proportions of the different polypeptides or proteins in biological samples, particularly human samples containing  
5 LAV or related viruses.

Thus all of the above peptides can be used in diagnostics as sources of immunogens or antigens free of viral particles, produced using non-permissive systems, and thus of little or no biohazard risk.

10 The invention further relates to the hosts (procar-  
yotic or eucaryotic cells) which are transformed by the above mentioned recombinants and which are capable of expressing said DNA fragments.

Finally it also relates to vaccine compositions  
15 whose active principle is to be constituted by any of the expressed antigens, i.e. whole antigens, fusion polypep-  
tides or oligopeptides in association with a suitable pharmaceutical or physiologically acceptable carrier.

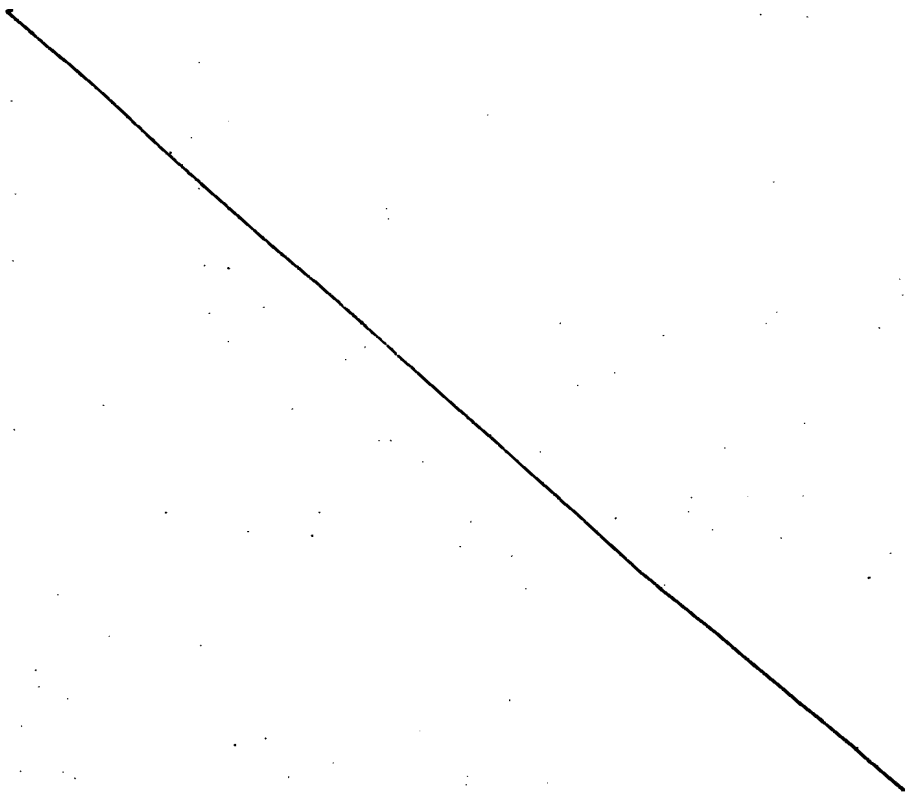
Preferably the active principles to be considered  
20 in that field consist of the peptides containing less than 250 aminoacid units, preferably less than 150 as deducible for the complete genomes of LAV, and even more preferably those peptides which contain one or more groups selected from N-X-S and N-X-T as defined above. Preferred peptides  
25 for use in the production of vaccinating principles are peptides (a) to (f) as defined above. By way of example having no limitative character, there may be mentioned that suitable dosages of the vaccine compositions are those which enable administration to the host,  
30 particularly human host ranging from 10 to 500 micrograms per kg, for instance 50 to 100 micrograms per kg.

For the purpose of clarity figs. 19 to 26 are added. reference may be made thereto in case of difficul-  
ties of reading blurred parts of figs. 4 to 12.

Needless to say that figs. 19-26 are merely a reiteration of the whole DNA sequence of the LAV genoma.

Finally the invention also concerns vectors for the transformation of eucaryotic cells of human origin, particularly lymphocytes, the polymerases of which are capable of recognizing the LTRs of LAV. Particularly said vectors are characterized by the presence of a LAV LTR therein, said LTR being then active as a promoter enabling the efficient transcription and translation in a suitable host of the above defined, of a DNA insert coding for a determined protein placed under its controls.

Needless to say that the invention extends to all variants of genomes and corresponding DNA fragments (ORFs) having substantially equivalent properties, all of said genomes belonging to retroviruses which can be considered as equivalents of LAV.



CLAIMS

1. A DNA fragment of LAV extending from nucleotide position 238 to nucleotide position 1759.
2. A DNA fragment of LAV extending from nucleotide position 1555 to nucleotide position 5086.
3. A DNA fragment of LAV extending from nucleotide position 5670 to nucleotide position 8132.
4. A vector containing a DNA fragment according to any of claims 1 to 3.
5. Peptide corresponding to any of those encoded by the nucleotide sequences which extend respectively between the following positions :
  - a) from about 6095 to about 6200
  - b) " " 6260 " " 6310
  - c) " " 6390 " " 6440
  - d) " " 6485 " " 6620
  - e) " " 6860 " " 6930
  - f) " " 7535 " " 7630
6. Peptide characterized by a sequence of amino-acids deducible from LAV DNA the terminal aminoacids of which extend between the following positions with respect to the lysine (position 1) coded by the AAA at position 5670-5672 in the LAV DNA.
 

	8-23 aminoacids inclusive
25	63-78 " "
	82-90 " "
	97-123 " "
	127-183 " "
	197-201 " "
30	239-294 " "
	300-327 " "
	334-381 " "
	397-424 " "
	466-500 " "
35	510-523 " "
	551-577 " "

	594-603	-	-
	621-630	-	-
	657-679	-	-
	719-758	-	-
5	780-803	-	-

or any combination of these peptides.

7. Peptide corresponding to the aminoacid sequences deducible from LAV DNA and the terminal aminoacids of which are positioned at the positions hereafter counted from the Met at position 1 coded by the ATG sequence at nucleotide positions 260-2 :

	12-32 aminoacids inclusive	
	37-46	- -
	49-79	- -
15	88-153	- -
	158-185	- -
	178-188	- -
	200-220	- -
	226-234	- -
20	239-264	- -
	288-331	- -
	352-361	- -
	377-390	- -
	399-432	- -
25	437-484	- -
	492-498	- -

and combination of said peptides.

8. Diagnostic means containing any of the DNA fragments of any of claims 1 to 3.

9. Diagnostic means containing any of the peptides of any of claims 4 to 6.

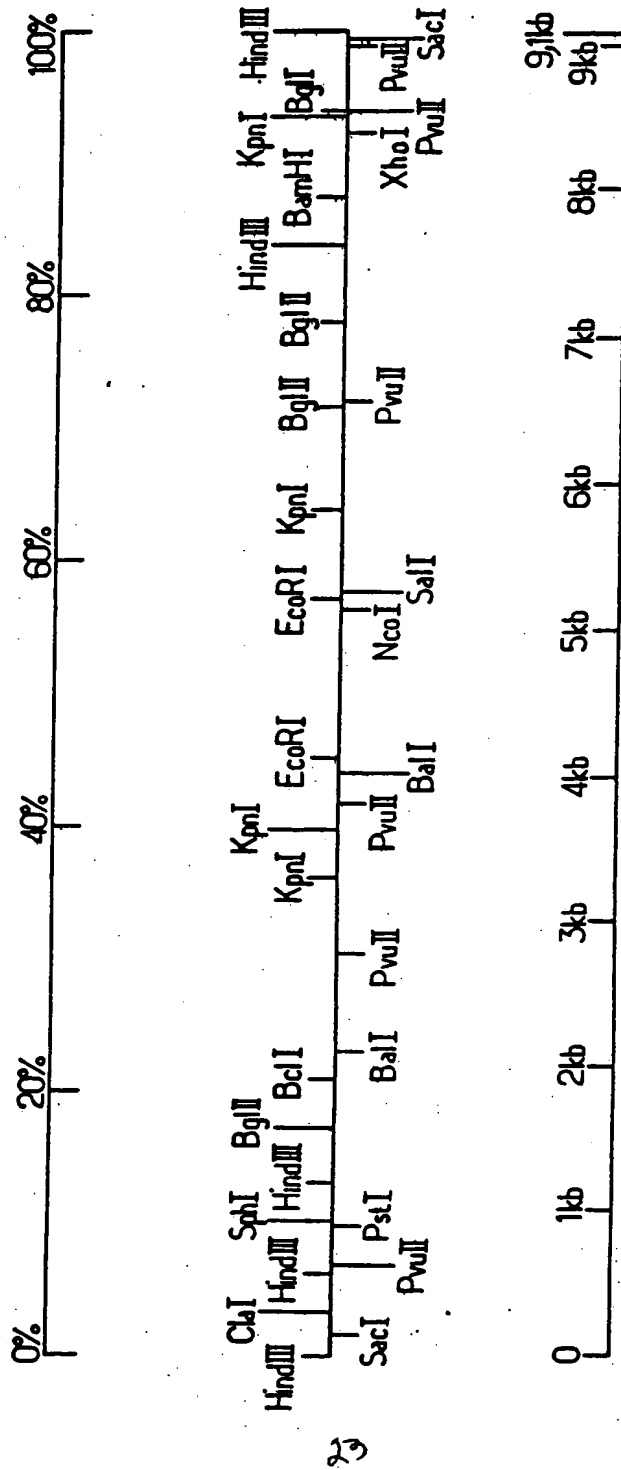
10. Vaccine compositions containing any of the peptides according to any of claims 4 to 6 in association with a pharmaceutical vehicle.

# ABSTRACT

This invention is in the field of lymphadenopathy virus. This invention relates to a diagnostic means and method to detect the presence of DNA, RNA or antibodies of the lymphadenopathy retrovirus associated with the acquired immune deficiency syndrome or of the lymphadenopathy syndrome by the use of DNA fragments or the peptides encoded by said DNA fragments. The invention further relates to the DNA fragments, vectors comprising them and the proteins expressed.

7/1240

FIG.1.



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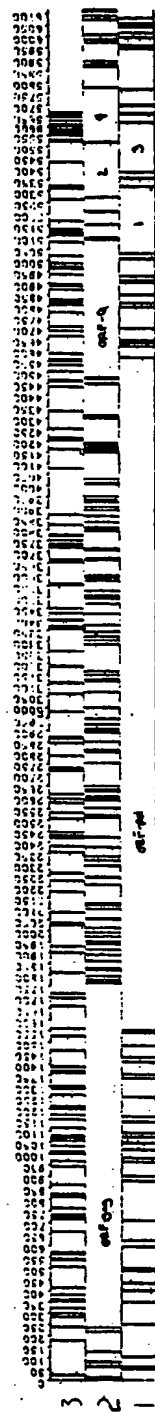


Fig. 2

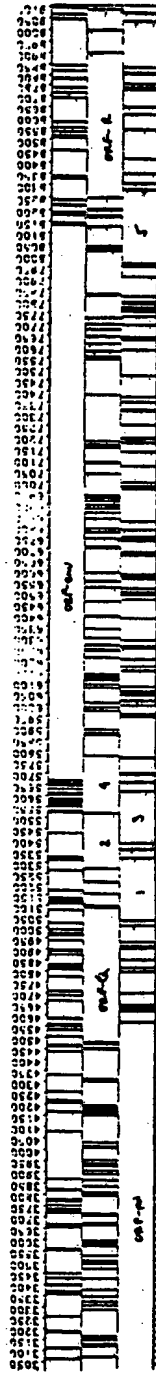


Fig. 3

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N L M I L K O O Y M O Y S S I L K E N C L C G I V C G N E P T P O O T  
 C G T S O S T M G S I M P O F O K M B G D W G C R G K N S N M S N A H  
 C A G G C T A C T C T T A G C A G C A T A C A A T G C C A T T C T C C A C A T T T T A A G C A A A G G G G C G A T T G C C G C C A A G C A C T C C A A G C A A T A T C A C A I N A T A C C A A G A C  
 4210 4220 4230 4240 4250 4260 4270 4280 4290 4300 4310 4320

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60P-Q

1 A V I D N S D I K V V P R K K I R D Y C K M A C D D C V A S R O D E  
2 S O Y R I V I A C U L A U S L C I M E R M V G V I V M O V N R  
3 S M R I O H S A K M S D H C L M E T D G B V L C K R T C G  
4 C A L T A C I A T A C A G A T A A A A G T A C C A C A A A G C A A G C A T T A G G A T T G C C A A G C A A G C A G C A G  
5 4470 4471 4472 4473 4474 4475 4476 4477 4478 4479 4480 4481 4482 4483 4484 4485 4486 4487 4488 4489 4490 4491 4492 4493 4494 4495 4496 4497 4498 4499 4500 4501 4502 4503 4504 4505 4506 4507 4508 4509 4510 4511 4512 4513 4514 4515 4516 4517 4518 4519 4520 4521 4522 4523 4524 4525 4526 4527 4528 4529 4530 4531 4532 4533 4534 4535 4536 4537 4538 4539 4540 4541 4542 4543 4544 4545 4546 4547 4548 4549 4550 4551 4552 4553 4554 4555 4556 4557 4558 4559 4560 4561 4562 4563 4564 4565 4566 4567 4568 4569 4570 4571 4572 4573 4574 4575 4576 4577 4578 4579 4580 4581 4582 4583 4584 4585 4586 4587 4588 4589 4590 4591 4592 4593 4594 4595 4596 4597 4598 4599 4600 4601 4602 4603 4604 4605 4606 4607 4608 4609 4610 4611 4612 4613 4614 4615 4616 4617 4618 4619 4620 4621 4622 4623 4624 4625 4626 4627 4628 4629 4630 4631 4632 4633 4634 4635 4636 4637 4638 4639 4640 4641 4642 4643 4644 4645 4646 4647 4648 4649 4650 4651 4652 4653 4654 4655 4656 4657 4658 4659 4660 4661 4662 4663 4664 4665 4666 4667 4668 4669 4670 4671 4672 4673 4674 4675 4676 4677 4678 4679 4680 4681 4682 4683 4684 4685 4686 4687 4688 4689 4690 4691 4692 4693 4694 4695 4696 4697 4698 4699 4700 4701 4702 4703 4704 4705 4706 4707 4708 4709 4710 4711 4712 4713 4714 4715 4716 4717 4718 4719 4720 4721 4722 4723 4724 4725 4726 4727 4728 4729 4730 4731 4732 4733 4734 4735 4736 4737 4738 4739 4740 4741 4742 4743 4744 4745 4746 4747 4748 4749 4750 4751 4752 4753 4754 4755 4756 4757 4758 4759 4760 4761 4762 4763 4764 4765 4766 4767 4768 4769 4770 4771 4772 4773 4774 4775 4776 4777 4778 4779 4780 4781 4782 4783 4784 4785 4786 4787 4788 4789 4790 4791 4792 4793 4794 4795 4796 4797 4798 4799 4800 4801 4802 4803 4804 4805 4806 4807 4808 4809 4810 4811 4812 4813 4814 4815 4816 4817 4818 4819 4820 4821 4822 4823 4824 4825 4826 4827 4828 4829 4830 4831 4832 4833 4834 4835 4836 4837 4838 4839 4840 4841 4842 4843 4844 4845 4846 4847 4848 4849 4850 4851 4852 4853 4854 4855 4856 4857 4858 4859 4860 4861 4862 4863 4864 4865 4866 4867 4868 4869 4870 4871 4872 4873 4874 4875 4876 4877 4878 4879 4880 4881 4882 4883 4884 4885 4886 4887 4888 4889 4890 4891 4892 4893 4894 4895 4896 4897 4898 4899 4900 4901 4902 4903 4904 4905 4906 4907 4908 4909 4910 4911 4912 4913 4914 4915 4916 4917 4918 4919 4920 4921 4922 4923 4924 4925 4926 4927 4928 4929 4930 4931 4932 4933 4934 4935 4936 4937 4938 4939 4940 4941 4942 4943 4944 4945 4946 4947 4948 4949 4950 4951 4952 4953 4954 4955 4956 4957 4958 4959 4960 4961 4962 4963 4964 4965 4966 4967 4968 4969 4970 4971 4972 4973 4974 4975 4976 4977 4978 4979 4980 4981 4982 4983 4984 4985 4986 4987 4988 4989 4990 4991 4992 4993 4994 4995 4996 4997 4998 4999 5000 5001 5002 5003 5004 5005 5006 5007 5008 5009 5010 5011 5012 5013 5014 5015 5016 5017 5018 5019 5020 5021 5022 5023 5024 5025 5026 5027 5028 5029 5030 5031 5032 5033 5034 5035 5036 5037 5038 5039 5040 5041 5042 5043 5044 5045 5046 5047 5048 5049 5050 5051 5052 5053 5054 5055 5056 5057 5058 5059 5060 5061 5062 5063 5064 5065 5066 5067 5068 5069 5070 5071 5072 5073 5074 5075 5076 5077 5078 5079 5080 5081 5082 5083 5084 5085 5086 5087 5088 5089 5090 5091 5092 5093 5094 5095 5096 5097 5098 5099 5100 5101 5102 5103 5104 5105 5106 5107 5108 5109 5110 5111 5112 5113 5114 5115 5116 5117 5118 5119 5120 5121 5122 5123 5124 5125 5126 5127 5128 5129 5130 5131 5132 5133 5134 5135 5136 5137 5138 5139 5140 5141 5142 5143 5144 5145 5146 5147 5148 5149 5150 5151 5152 5153 5154 5155 5156 5157 5158 5159 5160 5161 5162 5163 5164 5165 5166 5167 5168 5169 5170 5171 5172 5173 5174 5175 5176 5177 5178 5179 5180 5181 5182 5183 5184 5185 5186 5187 5188 5189 5190 5191 5192 5193 5194 5195 5196 5197 5198 5199 5200 5201 5202 5203 5204 5205 5206 5207 5208 5209 5210 5211 5212 5213 5214 5215 5216 5217 5218 5219 5220 5221 5222 5223 5224 5225 5226 5227 5228 5229 5230 5231 5232 5233 5234 5235 5236 5237 5238 5239 5240 5241 5242 5243 5244 5245 5246 5247 5248 5249 5250 5251 5252 52

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S A P T M S V L L O L F F R L C V K K G L I R I V S P P V O I S S  
V U P E L A U L I M L V T F H C F S A I P K A L L C H I V S P V C E V O A  
V T L N L I H F I C I L T F O L S O L E P P Y O L A L C V N I M O  
A U T A C C C C I G A N C I R C C A C C A N T A T C G T T A C T T A C G C T T A C C A G G C T T A T T A C C A G G C T T A T T A C C T A G C T T A C C T A G C T A T T A C C  
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Fig. 8





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Fig. 11



Fig 13

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V \* G E U E \* E H V D P R L E P W K H P G S O P V  
T F E S \* K \* S O \* I L D \* S P G S I O E V S L  
CAACAGAGGAGAGCAAGAAATGGAAGCAGTAGATCCTAGACTAGAGCCCTGGAAGCATCCAGGAAGTCAGCCTAA  
5290 5300 5310 5320 5330 5340 5350

P S L F H N K S L R H L L \* G E E A E T A T K T S  
O V C F T T K A L G I S Y G R K K R R Q R R R P P  
K F V S O O K P \* A S P H A G R S G D S D E D L  
CCAAGTTTGTTCACAACAAAAGCCTTAGGCATCTCCTATGGCAGGAAGACGGAGACAGCGACGAAGACCTCC  
5410 5420 5430 5440 5450 5460 5470

S T C N A T Y T N S N S S I S S S N N N S N S C V  
V H V M O P I U I A I A A L V V A I I I A I V V \*  
Y \* C N L Y K \* O \* O H \* \* \* O \* \* \* O \* L C  
AGTACATGTAATSCAACCTATACAAATAGCAATAGCAGCATTAGTAGTAGCAATAATAATAGCAATAGTTGTGTG  
5530 5540 5550 5560 5570 5580 5590

I \* U V N \* \* T N R K S R R O W O \* E \* R R N I S  
I U K L I O R L I E R A E D S G N E S E G E I S A  
\* T G \* L I O \* \* K E O K T V A M R V K E K Y U  
AATAGACAGGTTAATTGATAGACTAATAGAAAGAGCAGAAGACAGTGGCAATGAGAGTGAAGGAGAAATATCAGC  
5650 5660 5670 5680 5690 5700 5710

Y \* \* S V V L O K N C G S O S I M G Y L C G F K O  
I O D L \* C Y R K I V G H S L L W G T C V E G S N  
L M I C \* S A T E K L W V T V Y Y G V P V W K E A  
TATTGATGATCTGTAGTGCTACAGAAAAATTGTGGGTACAGTCTATTATGGGGTACCTGTGTGGAAGGAAGCAA  
5770 5780 5790 5800 5810 5820 5830

R Y I \* F G P H M P V Y P O T P T H K K \* Y \* \*  
G T \* C L G H T C L C T H R P O P T R S S I G V C  
V H N V W A T H A C V P T O P N P O E V V L V \*  
AGGTACATAATGTTTGGCCACACATGCCTGTGTACCCACAGACCCCAACCCACAAGCAAGTAGTATTGGTAAATC  
5890 5900 5910 5920 5930 5940 5950

C H R I \* S V Y G I K A \* S H V \* N \* P H S V L V  
A \* G Y N O F M G S K P K A M C K I N P T L C \* F  
H E D I I S L \* D O S L K P C V K L T P L C V S I  
TGCATGAGGATATAATCAGTTTATGGGATCAAAGCCTAAAGCCATGTGTAAAAATTAACCCCACTCTGTGTAGTTT  
6010 6020 6030 6040 6050 6060 6070

I P I V V A G K \* \* W R K E R \* K T A L S I S A O  
Y O \* \* \* K G H D D G E R R D K K I L F O Y O H K  
T \* S S S G E M M M E K G E I K \* N C S F \* N T S T  
ATACCAATAGTAGTACCGGGGAAATGATGATGGAGAAAGGAGAGATAAAAAACTGCTCTTTCAATATCAGGCACAA  
6130 6140 6150 6160 6170 6180 6190

L I \* Y O \* I M I L P A I R \* U V V T P U S L H R  
\* Y N T H R \* \* Y Y O L Y V O K L \* H L S H Y T G  
U I I P I O \* N D T T S Y T L T S C \* N T S V I T O A  
TTGATATAATACCAATAGATAATGATACTACCAGCTATACGTTGACAAGTTGTAACACCTCAGTCATTACACAGG  
6250 6260 6270 6280 6290 6300 6310

P R L V L R F \* N V I I R R S \* E O D H V O M S A

Fig 14

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G S Q P K T A C T T C Y C K K C C F H C  
Q E V S L K L L V P L A I V K S V A F I A  
AGGAAGTCAGCCTAAACTGCTTGACCACTTGCTATTGTAAAAAGTTGCTTTTCATTG  
5350 5360 5370 5380 5390 5400

A T K T S S R Q S D S S S F S I K A V S  
D R R P P Q G S G T H Q V S L S K O \* V  
S D E D L L K A V R L I K F L Y Q S S K \*  
AGCGACGAAGACCTCCTCAAGGCAGTCAGACTCATCAAGTTTCTCTATCAAAGCAGTAAGT  
5470 5480 5490 5500 5510 5520

S N S C V V H S N H R I \* E N I K T K K  
I A I V V W S I V I I E Y R K I L R O R K  
\* Q \* L C G P \* \* S \* N I G K Y \* D K E K  
TAGCAATAGTTGTGGTCCATAGTAATCATAGAATATAGGAAAATATTAAGACAAAGAAA  
5590 5600 5610 5620 5630 5640

R R N I S T C G D G G G N G A P C S L G  
G E I S A L V E M G V E M G H H A P W D  
K E K Y Q H L W R W G W K W G T M L L G I  
TAGGAGAAATATCAGCACTTGTTGGAGATGGGGGTGGAAATGGGGCACCATGCTCCTTGGGA  
5710 5720 5730 5740 5750 5760

C G F K Q P P L Y F V H Q M L K H M I Q  
V E G S N H H S I L C I R C \* S I \* Y R  
V W K E A T T T L F C A S D A K A Y D T E  
TGTGGAAGGAAGCAACCACCACTCTATTTTGTGCATCAGATGCTAAAGCATATGATACAG  
5830 5840 5850 5860 5870 5880

\* Y \* \* M \* Q K I L T C G K M T W \* N R  
V S I G K C D R K F \* H V E K \* H G R T D  
V V L V N V T E N F N M W K N D H V E Q M  
TAGTATTGGTAAATCTGACAGAAAATTTTAACATGTGGAATAATGACATGGGTAGACAGAA  
5950 5960 5970 5980 5990 6000

H S V L V \* S A L T W G \* L L I P I V V  
T L C \* F K V H \* F G E C Y \* Y O \* \*  
L C V S L K C T D L G N A T N T N S S N  
CACTCTGTGTTAGTTTAAAGTGCAGTATTTGGGGATGCTACTAATACCAATAGTAGTA  
6070 6080 6090 6100 6110 6120

S I S A Q A \* E V R C P K N M H F F I N  
Q Y Q H K H K R \* G A E R I C I F L \* T  
F N I S T S I R G K V G K E Y A F F Y K L  
TCAATATCAGCACAAGCATAAGAGGTAAGGTCCAGAAAGAAATATGCATTTTTTATAAAC  
6170 6200 6210 6220 6230 6240

U S L H R P V Q R Y P L S Q F P Y I I V  
S H Y T G L S K G I L \* A N S H T L L C  
S V I T O A C P K V S F E P I P I H Y C A  
CAGTCATTACACAGGCTGTCCAAAGGTATCCTTTGAGCCAATTCCCATACATTATTGTG  
6310 6320 6330 6340 6350 6360

V Q M S A Q Y N V H \* F L G Q \* Y Q L N

360

Fig 15

771248

P G W F C D S K Y \* | \* \* V J W N R T M Y K C Q  
P A G F A I L K C H N K T F N G T G P C T N V S  
CCCCGGCTGGTTTTGCGATTCTAAAAATGTAATAAAGACGTTCAATGGAACAGGACCATGTACAAATGTCAGG  
6370 6380 6390 6400 6410 6420 6430

C C \* N A V \* O K K R \* \* L D L P I S Q T N L K P  
A V E W O S S R R R G S N \* I C O F H R Q C \* N  
L L N G S L A E E E V V I R S A N F T D N A K T  
TUCTGTTCATGCCACTCTAGCAGAAGAAGAGGTAGTAATTAGATCTGCCAATTCACAGACAATGCTAAAACC  
6490 6500 6510 6520 6530 6540 6550

P T T I Q E K V S V S R G D Q G E H L L Q \* E K \*  
U Q Q Y K K K Y P Y P E G T R E S I C Y N R K N  
N N N T R K S I R I O R G P G R A F V T I G K I  
CCAACAACAATACAAGAAAAAGTATCCGTATCCAGAGGGGACCAGGGAGAGCATTGTTACAATAGGAAAAATA  
6610 6620 6630 6640 6650 6660 6670

M P L \* N R \* L A N \* E N N L E I I K Q \* S L S N  
C H F K T D S \* O I K R T I H K \* \* N N N L \* A  
A T L K Q I A S K L R E O F C N N K T I I F K Q  
ATGCCACTTTAAACAGATAGCTAGCAATTAAGAGAACAATTTGGAATAATAAAACAATAATCTTTAAGCAA  
6730 6740 6750 6760 6770 6780 6790

I G N F S T V I O H N C L I V L G L I V L G V L K  
R G I F L L \* F N T T V \* \* Y L V \* \* Y L E Y \*  
G E F F Y C N S T Q L F N S T W F N S T W S T E  
GAGGGGAATTTTCTACTGTAATTCACACAACGTGTTAATAGTACTTGGTTAATAGTACTTGGAGTACTGAAC  
6850 6860 6870 6880 6890 6900 6910

E \* N N L \* T C G R K \* E K Q C M P L P S A D K L  
N K T I Y K H V A G S R K S N V C P S H Q R T N \*  
I K O F I N M H O E V G K A M Y A P P I S G Q I  
GAATAAAACAATTTATAAACATGTGGCAGGAAGTAGGAAAAGCAATGTATGCCCTCCCATCAGCGGACAAATT  
6970 6980 6990 7000 7010 7020 7030

V I T T M G P R S S D L E E E I \* G T I G E V N Y  
\* \* O Q W V R D L O T W R R R Y E G O L E K \* I I  
N N N N G S E I F R P G G G O M R O N W R S E L  
GTAATAACAACAATGGGTCGAGATCTTCAGACCTGGAGGAGGAGATATGAGGGACAATTGGAGAAGTGAATTAT  
7090 7100 7110 7120 7130 7140 7150

P R Q R E E W C R E K K E Q W E \* E L C S L G S W  
O G K E K S G A E R K K S S G N R S F V P H V L G  
K A K R R V V Q R E K R A V G I G A L F L G F L  
CCAAGGCAAGAGAAGAGTGGTGCAGAGAGAAAAAGAGCAGTGGCAATAGGAGCTTTGTTCTTGGGTTCTTGG  
7210 7220 7230 7240 7250 7260 7270

Y R P O N Y C L V \* C S S R T I C \* G L L R R N S  
T G O T I I V W Y S A A A E Q F A E G Y \* G A T A  
Q A R O L L S G I V O Q Q N N L L R A I E A Q O  
TACAGGCCAGACAATTATTGTCTGTATAGTGCAGCACCAGACAATTTGCTGAGGGCTATTGAGGCGCAACAGC  
7330 7340 7350 7360 7370 7380 7390

E S A L H K D T \* R I N S S W G F G V A L E N S F

Fig. 16

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N R T M Y K C Q H S T M Y T W N \* A S S I N S T  
 T G P C T N V S T V O C T M G I R \* V V S T O L  
 AACAGGACCATGTACAAATGTCAGCACAGTACAATGTACACATGGAATTAGGCCAGTAGTATCAACTCAAC  
 6420 6430 6440 6450 6460 6470 6480

A I S O T M L K P \* \* Y S \* T N L \* K L I V U D  
 D F H R O C \* N H N S T A E P I C R N \* L Y K T  
 N F T D N A K T I I V O L N O S V E I N C T R P  
 CAATTTCAAGACAATGCTAAAACCATAATAGTACAGCTGAACCAATCTGTAGAAATTAATTTGTACAAGAC  
 6540 6550 6560 6570 6580 6590 6600

F H L L O \* E K \* E I \* D K H I V T L V F O N G  
 S I C Y N R K N R K Y E T S T L \* H \* S K M E  
 A F V T I G K I G N \* R Q A H C N I S R A K W N  
 AGCATTGTGTACATAGGAAAAATAGGAAATATGAGACAAGCACATTGTACATTAGTACAGCAAAATGCA  
 6640 6670 6680 6690 6700 6710 6720

I I K Q \* S L S N P O E G T O K L \* R T V L I V  
 \* \* N N V L \* A I L R R G P R N C N A O F \* L W  
 N K T I I F K O S S G G O P E I V T H S F N C G  
 TAATAAAACAATAATCTTTAAGCAATCCTCAGGAGGGGACCCAGAAATTGTAACGCACAGTTTAAATTGTG  
 6780 6790 6800 6810 6820 6830 6840

D L I V L G V L K G O I T L K E V T O S H S H A  
 V \* \* Y L E Y \* R V K \* H \* R K \* H V H T P M Q  
 F N S T W S T E G S N N T E G S O T I T L P C R  
 TTTAATAGTACTTGGAGTACTGAAGGGTCAATAACACTGAAGGAAGTGACACAATCACACTCCCATGCA  
 6900 6910 6920 6930 6940 6950 6960

\* P L P S A D K L D V H O I L O G C Y \* O E M V  
 C P S H O R T N \* M F I K Y Y R A A I N K R W  
 A P P I S G O I R C S S N I T G L L L T R D G G  
 TGGCCCTCCCATCAGCGGACAAATAGATGTTTCATCAAAATATTACAGGGCTGCTATTAACAAGAGATGGTG  
 7020 7030 7040 7050 7060 7070 7080

\* G T I G E V N Y I N I K \* \* K L N H \* E \* H P  
 E G O L E K \* I I \* I \* S S K N \* T I R S S T H  
 R O N W R S E L Y K Y K V V K I E P L G V A P T  
 CAGGCACAATTGGAGAAGTGAATTATATAAATATAAAGTAGTAAAAATTGAACCATAGGAGTAGCACCCA  
 7140 7150 7160 7170 7180 7190 7200

\* E L C S L G S H E O D E A L \* A H G O \* R \* R  
 R S F V P W V L G S S R K H Y G R T V N D A D G  
 G A L F L G F L G A A G S T M G A R S M T L T V  
 AGGAGCTTTGTTCTTGGGTTCTTGGGAGCAGCAGCAAGCACTATGGGGCAGCGTCAATGACGCTGACGG  
 7260 7270 7280 7290 7300 7310 7320

\* G L L R R N S I C C N S O S G A S S S S R O  
 A E G Y \* G A T A S V A T H S L G H D A A P G K  
 L R A I E A O O H L L O L T V W G I K O L O A R  
 CTGAGCGCTATTGACGGCCAACAGCATCTGTTGCAACTCACAGTCTGGGGCATCAAGCAGCTCCAGGCAA  
 7380 7390 7400 7410 7420 7430 7440

G V A L E N S F A P L L C L G \* L V G V I N L 28

Fig 17

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N P C C G K I P K G S T A P G D L G L L W K T M  
I L A V E R Y L K D O U L L G I W G C S G K L I  
GAATCCTGGCTGTGGAAGATACCTAAAGGATCAACAGCTCCTGGGGATTGGGGTTGCTCTGGAAGAACTCAT  
7450 7460 7470 7480 7490 7500 7510

W N R F G I T \* P G W S G T E K L T I T O A \* Y  
G T D L E \* H D L D G V G O R N \* O L M K L N T  
E O I W N N H Y W M E W D R E I N N Y T S L I H  
TGGAACAGATTGGGAATAACATGACCTGGATGGAGTGGGACAGAGAAATTAACAATTACACAAGCTTAATACA  
7570 7580 7590 7600 7610 7620 7630

N Y W N \* I N G O V C G I G L T \* O I G C G I \*  
I I G I R \* M G K F V E L V \* H N K L A V V Y K  
L L E L D K W A S L W N W F N I T N W L W Y I K  
AATTATTGGAATTAGATAAATGGGCAAGTTTGTGGAATTGCTTTAACAATAAATGGCTGTGCTATATAAA  
7690 7700 7710 7720 7730 7740 7750

L L Y F L \* \* I E L G R D I H H Y R F R P T S Q I  
C C T F Y S E \* S \* A G G I F T I I V S D P P P N  
A V L S I V / N R V R O G Y S P L S F O T H L P T  
TTGCTGTACTTTCTATAGTGAATAGAGTTAGGCAGGGATATTACCATTATCGTTTCAGACCCACCTCCCAACI  
7810 7820 7830 7840 7850 7860 7870

R E T E T D P F D \* \* T D P \* H L S G T I C G A I  
E R U P Q I H S I S E R I L S T Y L G R S A E P  
R D R D R S I R L V N G S L A L I W D D L R S L  
AGAGAGACAGACAGATCCATTGATTAGTGAACGGATCCTTAGCACTTATCTGGGACGATCTGCCGAGCCT  
7930 7940 7950 7960 7970 7980 7990

T R I V E L L G R G H E A L K Y W W N L L O Y  
R G L W N F W D A G G G K P S N I G G I S Y S I  
E D C G T S G T O G V G S P O I L V E S P T V L  
ACGAGCATTGTGGAACCTTCTGGGACCCAGGGGGTGGGAAGCCCTCAAAATATTGGTGGAAATCTCTACAGTATT  
8050 8060 8070 8080 8090 8100 8110

A I A V A E G T D R V I E V V O G A C R A I R H I  
P \* J \* L R G Q I G L \* K \* Y K E L V E L F A T  
H S S S \* G D R \* G Y R S S T R S L \* S Y S P H  
GCCATAGCAGTAGCTGAGGGGACAGATAGGGTTATAGAAGTAGTACAAGGACCTGTAGAGCTATTGCCACAT  
8170 8180 8190 8200 8210 8220 8230

G W O V V K K \* C G W H A Y C K G K V E T S \* A S  
G G K W S K S S V V G W P T V R E R M R A E P  
V A S G O K V V W L D G L L \* G K E \* D E L S O  
GGGTGGCAAGTGGTCAAAAAGTAGTGTGCTTGGATGGCCTACTGTAAGGGAAGAATGAGACGAGCTGAGCCAG  
8290 8300 8310 8320 8330 8340 8350

S N H K \* O Y S S Y O C C L C L A R S T R G G G G  
A I T S S H T A A T N A A C A W L F A O E E E E  
O S O V A I U O L P N L L V P G \* K H K R R R  
ACCAATCACAAGTAGCAATACAGCAGCTACCAATGCTGCTTGGCTGGCTTGAAGGACAGAGGAGGAGGAGG  
8410 8420 8430 8440 8450 8460 8470

U G S C R S \* P L F K R K G G T G

CH/ A H S L P K  
15/15

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Fig 18

A K T H L H H C G A L E C \* L E \* \* I S  
G K L M I C T T A V P W N A S M S N K L  
TTGGAAACTCATTTCACCACTGCTGTGCCTTGGAAATGCTAGTTGGAGTAATAAATCTC  
7510 7520 7530 7540 7550 7560

Q A \* Y I P \* L K N R K T S K K R M N K  
K L N T F L N \* R I A K P A R K E \* T R  
S L I H S L I E E S O V O O E K N E O E  
AAGCTTAATACATTCTTAATTGAAGAATCGCAAAACCAGCAAGAAAAGAATGAACAAG  
7630 7640 7650 7660 7670 7680

C G I \* K Y S \* \* \* \* E A W \* V \* E \* F  
V V Y K N I H N D S R R L G R F K N S F  
W Y I K I F I M I V G G L V G L / R / I V F  
GTGGTATATAAAATATTCAATGATAGTAGGAGGCTTGCTAGGTTTAAGAATAGTTT  
7750 7760 7770 7780 7790 7800

P T S Q P R G D P T G P K E \* K K K V E  
P P P N P E G T R O A R R N R R R R W R  
H L P T P R G P D R P E G I E E E G G E  
CCACCTCCCAACCCCGAGGGGACCCGACAGGCCCGAAGGAATAGAAGAAGGTGGAG  
7870 7880 7890 7900 7910 7920

I C G A L C L F S Y H R L R D L L L I V  
S A E P C A S S A T T A \* E T Y S \* L \*  
L R S L V P L O L P P L E R L T L D C N  
TCTGCCGAGCCTTGTGCTCTTCAGCTACCACCGCTTGAGAGACTTACTCTTGATTGTA  
7990 8000 8010 8020 8030 8040

L L O Y H S O E L K N S A V S L L N A T  
S Y S I G V R N \* R I V L L A C S M P O  
P T V L E S G T K E \* C C \* L A O C H S  
TCCTACAGTATTGGAGTCAGGAACATAAGAATAGTGCTGTTAGCTTGCTCAATGCCACA  
8110 8120 8130 8140 8150 8160

A I R H I P R R I R O G L E R I L L \* D  
L F A T Y L E E \* D R A W K G F C Y K M  
Y S P H T \* K N K T G L G K O F A I R W  
CTATTGCCACATACCTAGAAGAATAAGACAGGGCTTGGAAAGGATTTTGCTATAAGAT  
8230 8240 8250 8260 8270 8280

T S \* A S S R \* G G S S I S R P G K T W  
R A E P A A D G V G A A S R D L E K H G  
E L S O O \* G W E O H L E T W K N M E  
GAGCTGAGCCAGCAGCAGATGGGGTGGGAGCAGCATCTCGAGACCTGGAAAAACATGG  
8350 8360 8370 8380 8390 8400

G G G G G F S S H T S G T F K T N D L  
E E E E V G F P V T P C V P L R P M T Y  
R R R R Y F S H L R Y L \* D O \* L T  
AGGACGAGGAGG GGG TTTCCAGTCACACCTCAGGTAGCTTTAAGACCAATGACTTA  
8470 8480 8490 8500 8510 8520

L P T A \* S V D L P H T R L L  
15/15 B/14

Fig 19

10 20 30 40 50 60  
AAGCTTGCTT TGAGTGCTTC AAGTAGTG TGCCCGTCTG TTGTGTGACT CTGGTAACATA

70 80 90 100 110 120  
GAGATCCCTC AGACCCTTTT AGTCAGTG TGAAAATCTCT AGCAGTGCGG CCCGAACAGG

130 140 150 160 170 180  
GACTTGAAAG CGAAAGGGAA ACCAGAGGAG CTCTCTCGAC GCAGGACTCG GCTTGCTGAA

190 200 210 220 230 240  
GCGCGCACGG CAAGAGGCGA GGGGAGGCGA CTGGTGAGTA CGCCAAAAAT TTTGACTAGC

250 260 270 280 290 300  
GGAGGCTAGA AGGAGAGAGA TGGGTGCCAG AGCCTCAGTA TTAAGCGGGG GAGAATTAGA

310 320 330 340 350 360  
TCGATGGGAA AAAATTCTGGT TAAGGCCAGG GGGAAAGAAA AAATATAAAT TAAAACATAT

370 380 390 400 410 420  
AGTATGGGCA AGCAGGGAGC TAGAACGATT CGCTGTTAAT CCTGGCCTGT TAGAAACATC

430 440 450 460 470 480  
AGAAGGCTGT AGACAAATAC TGGGACAGCT ACAACCATCC CTTGAGACAG GATCAGAAGA

490 500 510 520 530 540  
ACTTAGATCA TTATATAATA CAGTAGCAAC CCTCTATTGT GTGCATCAAA GGATAGAGAT

550 560 570 580 590 600  
AAAAGACACC AAGGAAGCTT TAGACAAGAT AGAGGAAGAG CAAAACAAAA GTAAGAAAAA

610 620 630 640 650 660  
AGCACAGCAA GCAGCAGCTG ACACAGGACA CAGCAGCCAG GTCAGCCAAA ATTACCTAT

670 680 690 700 710 720  
ACTGCAGAAC ATCCAGGGGC AAATGGTACA TCAGGCCATA TCACCTAGAA CTTTAAATGC

730 740 750 760 770 780  
ATGGGTAAAA GTAGTAGAAG AGAAGGCTTT CAGCCCAGAA GTGATACCCA TGTTTTCAGC

790 800 810 820 830 840  
ATTATCAGAA GGAGCCACCC CACAAGATT AAACACCATG CTAAACACAG TGGGGGGACA

850 860 870 880 890 900  
TCAAGCAGCC ATGCAAATGT TAAAAGAGAC CATCAATGAG GAACCTGCAG AATGGGATAG

910 920 930 940 950 960  
AGTGCATCCA GTGCATGCAG GGCCTATTGC ACCAGGCCAG ATGAGAGAAC CAAGGGGAAG

970 980 990 1000 1010 1020  
TGACATAGCA GGAACACTA GTACCCTTCA GGAACAAATA GGATGGATGA CAAATAATCC

1030 1040 1050 1060 1070 1080  
ACCTATCCCA GTAGGAGAAA TTTATAAAG ATGGATAATC CTGGGATTAA ATAAAATAGT

1090 1100 1110 1120 1130 1140

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Fig 20

AAATAATGTAT	AGCCCTACCA	GCATTCTGGA	CATAAGAÇAA	GGACCAAAAAG	AACCCCTTTAG
1150	1160	1170	1180	1190	1200
AGACTATGTA	GACCGGTTCT	ATAAAACTCT	AAGAGCCGAG	CAAGCTTCAC	AGGAGGTAAA
1210	1220	1230	1240	1250	1260
AAATTGGATG	ACAGAAACCT	TGTTGGTCCA	AAATGCCAAC	CCAGATTGTA	AGACTATTTT
1270	1280	1290	1300	1310	1320
AAAAGCATTG	GGACCAGCAG	CTACACTAGA	AGAAATGATG	ACAGCATGTC	AGGGAGTGGG
1330	1340	1350	1360	1370	1380
AGGACCCGGC	CATAAGGCAA	CAGTTTTGGC	TGAAGCAATG	AGCCAAGTAA	CAAATTCAGC
1390	1400	1410	1420	1430	1440
TACCATAATG	ATGCAAAGAG	GCAATTTTAG	GAACCAAAGA	AAGATTGTTA	AGTGTTCCTA
1450	1460	1470	1480	1490	1500
TTGTGGCAAA	GAAGGGCACA	TAGCCAGAAA	TTGCAGGGCC	CCTAGGAAAA	AGGGCTGTTG
1510	1520	1530	1540	1550	1560
GAAATGTGGA	AAGGAAGGAC	ACCAAATGAA	AGATTGTACT	GAGAGACAGG	CTAATTTTTT
1570	1580	1590	1600	1610	1620
AGGGAAGATC	TGGCCTTCCT	ACAAGGGAAG	GCCAGGGAAT	TTTCTTCAGA	GCAGACCAGA
1630	1640	1650	1660	1670	1680
GCCAACAGCC	CCACCAGAAG	AGAGCTTCAG	GTCTGGGGTA	GAGACAACAA	CTCCCTCTCA
1690	1700	1710	1720	1730	1740
GAAGCAGGAG	CCGATAGACA	AGGAACGTGA	TCCTTTAACT	TCCCTCAGAT	CACTCTTTGG
1750	1760	1770	1780	1790	1800
CAACGACCCC	TCGTACACAAT	AAAGATAGGG	GGGCAACTAA	AGGAAGCTCT	ATTAGATACA
1810	1820	1830	1840	1850	1860
GGAGCAGATG	ATACAGTATT	AGAAGAAATG	AGTTTGCCAG	GAAGATGGAA	ACCAAAAATG
1870	1880	1890	1900	1910	1920
ATAGGGGGAA	TTGGAGGTTT	TATCAAAGTA	AGACAGTATG	ATCAGATACT	CATAGAAATG
1930	1940	1950	1960	1970	1980
TGTGGACATA	AAGCTATAGG	TACAGTATTA	GTAGGACCTA	CACCTGTCAA	CATAATTGGA
1990	2000	2010	2020	2030	2040
AGAAATCTGT	TGACTCAGAT	TGGTTGCACT	TTAAATTTTC	CCATTAGTCC	TATTGAAACT
2050	2060	2070	2080	2090	2100
GTACCAGTAA	AATTAAAGCC	AGGAATGGAT	GGCCCAAAAG	TTAAACAATG	CCCATTGACA
2110	2120	2130	2140	2150	2160
GAAGAAAAAA	TAAAGCATT	AGTAGAAAAT	TGTACAGAAA	TGGAAAAGGA	AGGGAAAAAT
2170	2180	2190	2200	2210	2220
TCAAAAATTG	GGCCTGAAAA	TCCATACAAT	ACTCCAGTAT	TTGCCATAAA	GAAAAAAGAC
2230	2240	2250	2260	2270	2280
AGTACTAAAT	GGAGAAAATT	AGTAGATTTT	AGAGAACTTA	ATAAGAGAAC	TCAAGACTTC
2290	2300	2310	2320	2330	2340
TGGGAAGTTC	AATTAGGAAT	ACCACATCCC	GCAGGGTTAA	AAAAGAAAAA	ATCAGTAACA
2350	2360	2370	2380	2390	2400

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GTCGTGATTC TGGGTGATGC ATATTTTTC GTTCCCTTAG ATGAAGACTT CAGGAAGTAT  
 2410 2420 2430 2440 2450 2460  
 ACTGCATTTA CCATACCTAG TATAAACAAT GAGACACCAG GGATTAGATA TCACTACAAT  
 2470 2480 2490 2500 2510 2520  
 GTGCTTCCAC AGGGATGGAA AGGATCACCA GCAATATTCC AAAGTAGCAT GACAAAAATC  
 2530 2540 2550 2560 2570 2580  
 TTAGAGCCTT TTAGAAAAACA AAATCCAGAC ATAGTTATCT ATCAATACAT CGATGATTTG  
 2590 2600 2610 2620 2630 2640  
 TATGTAGGAT CTGACTTAGA AATAGGGCAG CATAGAACAA AAATAGAGGA GCTGAGACAA  
 2650 2660 2670 2680 2690 2700  
 CATCTGTTGA GGTGGGGACT TACCACACCA GACAAAAAAC ATCAGAAAGA ACCTCCATTG  
 2710 2720 2730 2740 2750 2760  
 CTTTGGATGG GTTATGAACT CCATCCTGAT AAATGGACAG TACAGCCTAT AGTGCTGCCA  
 2770 2780 2790 2800 2810 2820  
 GAAAAAGACA GCTGGACTGT CAATGACATA CAGAAGTTAG TGGGAAAATT GAATTGGGCA  
 2830 2840 2850 2860 2870 2880  
 AGTCAGATTT ACCCAGGGAT TAAAGTAAGG CAATTATGTA AACTCCTTAG AGGAACCAAA  
 2890 2900 2910 2920 2930 2940  
 GCACTAACAG AAGTAATACC ACTAACAGAA GAAGCAGAGC TAGAACTGGC AGAAAAACAGA  
 2950 2960 2970 2980 2990 3000  
 GAGATTCTAA AAGAACCAGT ACATGGAGTG TATTATGACC CATCAAAAAGA CTTAATAGCA  
 3010 3020 3030 3040 3050 3060  
 GAAATACAGA AGCAGGGGCA AGGCCAATGG ACATATCAAA TTTATCAAQA GCCATTTAAA  
 3070 3080 3090 3100 3110 3120  
 AATCTGAAAA CAGGAAAAATA TGCAAGAACG AGGGGTGCCC AACTAATGA TGTA AAAACAA  
 3130 3140 3150 3160 3170 3180  
 TTAACAGAGG CAGTGCAAAA AATAACCACA GAAAGCATAG TAATATGGGG AAAGACTCCT  
 3190 3200 3210 3220 3230 3240  
 AAATTTAAAC TACCCATACA AAAGGAAACA TGGGAAACAT GGTGGACAGA GTATTGGCAA  
 3250 3260 3270 3280 3290 3300  
 GCCACCTGGA TTCCTGAGTG GGAGTTTGTC AATACCCCTC CTTTAGTGAA ATTATGGTAC  
 3310 3320 3330 3340 3350 3360  
 CAGTTAGAGA AAGAACCCAT AGTAGGAGCA GAAACGTTCT ATGTAGATGG GGCAGCTAGC  
 3370 3380 3390 3400 3410 3420  
 AGGGAGACTA AATTAGGAAA AGCAGGATAT GTTACTAATA GAGGAAGACA AAAAGTTGTC  
 3430 3440 3450 3460 3470 3480  
 ACCCTAACTG ACACAACAAA TCAGAAGACT GAGTTACAAG CAATTCATCT AGCTTTGCAG  
 3490 3500 3510 3520 3530 3540  
 GATTGGGGAT TAGAAGTAAA TATAGTAACA GACTCACAAT ATGCATTAGG AATCATTCAA  
 3550 3560 3570 3580 3590 3600  
 GCACAACCAG ATAAAAGTGA ATCAGAGTTA GTCAATCAAA TAATAGAGCA GTTAATAAAA  
 3610 3620 3630 3640 3650 3660

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Fig 22

3670 3680 3690 3700 3710 3720  
 GTAGATAAAT TAGTCAGTGC TGGCAATCAGG AAAGTACTAT TTTTAGATGG AATAGATAAG  
 3730 3740 3750 3760 3770 3780  
 GCCCAAGATG AACATGAGAA ATATCACAGT AATTGGAGAG CAATGGCTAG TGATTTTAAC  
 3790 3800 3810 3820 3830 3840  
 CTGCCACCTG TAGTAGCAAA AGAAATAGTA GCCAGCTGTG ATAAATGTCA GCTAAAAGGA  
 3850 3860 3870 3880 3890 3900  
 GAAGCCATGC ATGGACAAGT AGACTGTAGT CCAGGAATAT GGCAACTAGA TTGTACACAT  
 3910 3920 3930 3940 3950 3960  
 TTAGAAGGAA AAGTTATCCT GGTAGCAGTT CATGTAGCCA GTGGATATAT AGAAGCAAGAA  
 3970 3980 3990 4000 4010 4020  
 GTTATTCCAG CAGAAACAGG GCAGGAAACA GCATACTTTC TTTTAAAATT AGCAGGAAGA  
 4030 4040 4050 4060 4070 4080  
 TGGCCAGTAA AAACAATACA TACAGACAAT GGCAGCAATT TCACCAGTAC TACGGTTAAG  
 4090 4100 4110 4120 4130 4140  
 GCCGCCTGTT GGTGGGCGGG AATCAAGCAG GAATTTGGAA TTCCCTACAA TCCCCAAAGT  
 4150 4160 4170 4180 4190 4200  
 CAAGGAGTAG TAGAATCTAT GAATAAGAA TTAAGAGAAA TTATAGGCCA GGTAAGAGAT  
 4210 4220 4230 4240 4250 4260  
 CAGGCTGAAC ATCTTAAGAC AGCAGTACAA ATGGCAGTAT TCATCCAACA TTTTAAAAGA  
 4270 4280 4290 4300 4310 4320  
 AAAGGGGGGA TTGGGGGGTA CAGTGCAAGG GAAAGAATAG TAGACATAAT AGCAACAGAC  
 4330 4340 4350 4360 4370 4380  
 ATAÇAAACTA AAGAATTACA AAAACAAATT ACAAAAAATC AAAATTTTCG GGTTTATTAC  
 4390 4400 4410 4420 4430 4440  
 AGGGACAGCA GAGATCCACT TTGGAAAGGA CCAGCAAAGC TCCTCTGGAA AGGTGAAGGG  
 4450 4460 4470 4480 4490 4500  
 GCAGTAGTAA TACAAGATAA TAGTGACATA AAAGTAGTGC CAAGAAGAAA AGCAAAGATC  
 4510 4520 4530 4540 4550 4560  
 ATTAGGGATT ATGGAAAACA GATGGCAGGT GATGATTCTG TGGCAAGTAG ACAGGATGAG  
 4570 4580 4590 4600 4610 4620  
 GATTAGAACA TGGAAAAGTT TAGTAAAACA CCATATGTAT GTTTCAGGGA AAGCTAGGGG  
 4630 4640 4650 4660 4670 4680  
 ATGGTTTTAT AGACATCACT ATGAAAGCCC TCATCCAAGA ATAAGTTTAC AAGTACACAT  
 4690 4700 4710 4720 4730 4740  
 CCCACTAGGG GATGCTAGAT TGGTAATAAC AACATATTGG GGTCTGCATA CAGGAGAAAG  
 4750 4760 4770 4780 4790 4800  
 AGACTGGCAT CTGGGTCAGG GAGTCTCCAT AGAATGGAGG AAAAAGAGAT ATAGCACACA  
 4810 4820 4830 4840 4850 4860  
 AGTAGACCCT GAACTAGCAG ACCAACTAAT TCATCTGTAT TACTTTGACT GTTTTTCAGA  
 4870 4880 4890 4900 4910 4920

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CTCTCTATA AGAAAGGCTT TATTAGGACA TATAGTTAGC CCTAGGTGTG AATATCAAGC  
 4930 4940 4950 4960 4970 4980  
 AGGACATAAC AAGGTAGGAT CTCTACAATA CTTGGGACTA GCAGCATTAA TAACACCAAA  
 4990 5000 5010 5020 5030 5040  
 AAAGATAAAG CCACCTTTGC CTAGTGTTAC GAAACTGACA GAGGATAGAT GGAACAAGCC  
 5050 5060 5070 5080 5090 5100  
 CCAGAAGACC AAGGGCCACA GAGGGAGCCA CACAATCAAT GGACACTAGA GCTTTTAGAG  
 5110 5120 5130 5140 5150 5160  
 GAGCTTAAGA ATGAAGCTGT TAGACATTTT CCTAGGATTT GGCTCCATGG CTTAGGGCAA  
 5170 5180 5190 5200 5210 5220  
 CATATCTATG AAACCTTATGG GGATACTTGG GCAGGAGTGG AAGCCATAAT AAGAATTCTG  
 5230 5240 5250 5260 5270 5280  
 CAACAACCTGC TGTTTATCCA TTTGAGAAAT GGGTGTGAC ATAGCAGAAT AGGCGTTACT  
 5290 5300 5310 5320 5330 5340  
 CAACAGAGGA GAGCAAGAAA TGGAGCCACT AGATCCTAGA CTAGAGCCCT GGAAGCATCC  
 5350 5360 5370 5380 5390 5400  
 AGGAAGTCAG CCTAAACTG CTTGTACCAC TTGCTATTGT AAAAAAGTGT GCTTTCATTG  
 5410 5420 5430 5440 5450 5460  
 CCAAGTTTGT TTCACAACAA AAGCCTTAGG CATCTCCTAT GGCAGGAAGA AGCGGAGACA  
 5470 5480 5490 5500 5510 5520  
 GCGACGAAGA CCTCCTCAAG GCAGTCAGAC TCATCAAGTT TCTCTATCAA AGCAGTAAGT  
 5530 5540 5550 5560 5570 5580  
 AGTACATGTA ATGCAACCTA TACAAATAGC AATAGCAGCA TTAGTAGTAG CAATAATAAT  
 5590 5600 5610 5620 5630 5640  
 AGCAATAGTT GTGTGGTCCA TAGTAATCAT AGAATATAGC AAAATATTAA GACAAAGAAA  
 5650 5660 5670 5680 5690 5700  
 AATAGACAGG TTAATTGATA GACTAATAGA AAGAGCAGAA GACAGTGGCA ATGAGAGTGA  
 5710 5720 5730 5740 5750 5760  
 AGGAGAAATA TCAGCACTTG TGGAGATGGG GGTGGAAATG GGGCACCATG CTCCTTGGGA  
 5770 5780 5790 5800 5810 5820  
 TATTGATGAT CTGTAGTGCT ACAGAAAAAT TGTGGGTCAC AGTCTATTAT GGGGTACCTG  
 5830 5840 5850 5860 5870 5880  
 TGTGGAAGGA AGCAACCACC ACTCTATTTT GTGCATCAGA TGCTAAAGCA TATGATACAG  
 5890 5900 5910 5920 5930 5940  
 AGGTACATAA TGTTTGGGCC ACACATGCCT GTGTACCCAC AGACCCCAAC CCACAAGAAG  
 5950 5960 5970 5980 5990 6000  
 TAGTATTGGT AAATGTGACA GAAAAATTTA ACATGTGGAA AAATGACATG GTAGAACAGA  
 6010 6020 6030 6040 6050 6060  
 TGCATGAGGA TATAATCAGT TTATGGGATC AAAGCCTAAA GCCATGTGTA AAATTAACCC  
 6070 6080 6090 6100 6110 6120  
 CACTCTGTGT TAGTTTAAAG TGGACTGATT TGGGGAATGC TACTAATACC AATAGTAGTA  
 6130 6140 6150 6160 6170 6180

Fig 23

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ATACCAATAG TAGTAGCGGG GAAATGATGA TGGAGAAAGG AGAGATAAAA AACTGCTCTT  
 6170 6200 6210 6220 6230 6240  
 TCAATATCAG CACAAGCATA AGAGGTAAGG TCCAGAAAGA ATATGCATT TTTTATAAAC  
 6250 6260 6270 6280 6290 6300  
 TTGATATAAT ACCAATAGAT AATGATACTA CCAGCTATAC GTTGACAAGT TGTAACACCT  
 6310 6320 6330 6340 6350 6360  
 CAGTCATTAC ACAGGCCTGT CCAAAGGTAT CCTTGAGCC AATTCCCAT CATTATTGTG  
 6370 6380 6390 6400 6410 6420  
 CCCCCGCTGG TTTTGGCATT CTAAAATGTA ATAATAAGAC GTTCAATGGA ACAGGACCAT  
 6430 6440 6450 6460 6470 6480  
 GTACAAATGT CAGCACAGTA CAATGTACAC ATGGAATTAG GCCAGTAGTA TCAACTCAAC  
 6490 6500 6510 6520 6530 6540  
 TGCTGTTGAA TGGCAGTCTA GCAGAAGAAG AGGTAGTAAT TAGATCTGCC AATTTACAG  
 6550 6560 6570 6580 6590 6600  
 ACAATGCTAA AACCATAATA GTACAGCTGA ACCAATCTGT AGAAATTAAT TGTACAAGAC  
 6610 6620 6630 6640 6650 6660  
 CCAACAACAA TACAAGAAAA AGTATCCGTA TCCAGAGGGG ACCAGGGAGA GCATTTGTTA  
 6670 6680 6690 6700 6710 6720  
 CAATAGGAAA AATAGGAAAT ATGAGACAAG CACATTGTAA CATTAGTAGA GCAAAATGCA  
 6730 6740 6750 6760 6770 6780  
 ATGCCACTTT AAAACAGATA GCTAGCAAAT TAAGAGAACA ATTTGGAAAT AATAAAACAA  
 6790 6800 6810 6820 6830 6840  
 TAATCTTTAA GCAATCCTCA GGAGGGGACC CAGAAATTGT AACCCACAGT TTTAATTGTG  
 6850 6860 6870 6880 6890 6900  
 GAGGGGAATT TTTCTACTGT AATTCAACAC AACTGTTTAA TAGTACTTGG TTTAATAGTA  
 6910 6920 6930 6940 6950 6960  
 CTTGGAGTAC TGAAGGGTCA AATAACACTG AAGGAAGTGA CACAATCACA CTCCCATGCA  
 6970 6980 6990 7000 7010 7020  
 GAATAAAACA ATTTATAAAC ATGTGGCAGG AAGTAGGAAA AGCAATGTAT GCCCCTCCCA  
 7030 7040 7050 7060 7070 7080  
 TCAGCGGACA AATTAGATGT TCATCAAATA TTACAGGGCT GCTATTAACA AGAGATGCTG  
 7090 7100 7110 7120 7130 7140  
 GTAATAACAA CAATGGGTCC GAGATCTTCA GACCTGGAGG AGGAGATATC AGGGACAATT  
 7150 7160 7170 7180 7190 7200  
 GGAGAAGTGA ATTATATAAA TATAAAGTAG TAAAAATTGA ACCATTAGGA GTAGCACCCA  
 7210 7220 7230 7240 7250 7260  
 CCAAGGCAAA GAGAAGAGTG GTGCAGAGAG AAAAAAGAGC AGTGGGAATA GGAGCTTTGT  
 7270 7280 7290 7300 7310 7320  
 TCCTTGGGTT CTTGGGAGCA GCAGGAAGCA CTATGGGCGC ACGGTCAATG ACGCTGACGG  
 7330 7340 7350 7360 7370 7380  
 TACAGGCCAG ACAATTATTG TCTGGTATAG TGCAGCAGCA GAACAATTG CTGAGGGCTA  
 7390 7400 7410 7420 7430 7440

7824

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TTGAGGCGCA ACAUCATCTG TTGCAACTCA CAGTCTGGGG CATCAAGCAG CTCCAGGCAA

7450 7460 7470 7480 7490 7500  
GAATCCTGGC TGTGGAAAGA TACCTAAAGG ATCAACAGCT CCTGGGGATT TGGGGTTGCT

7510 7520 7530 7540 7550 7560  
CTGGAAACT CATTTCACCC ACTGCTGTGC CTTGGAATGC TAGTTGGAGT AATAAATCTC

7570 7580 7590 7600 7610 7620  
TGAACAGAT TTGGAATAAC ATGACCTGGA TGAGTGGGA CAGAGAAATT AACAATTACA

7630 7640 7650 7660 7670 7680  
CAAGCTTAAT ACATTCTTA ATTGAAGAAT CGCAAAACCA GCAAGAAAAG AATGAACAAG

7690 7700 7710 7720 7730 7740  
AATTATTGGA ATTAGATAAA TGGGCAAGTT TGTGGAATTG GTTTAACATA ACAAATTGGC

7750 7760 7770 7780 7790 7800  
TGTGGTATAT AAAAATATTC ATAATGATAG TAGGAGGCTT GGTAGGTTTA AGAATAGTTT

7810 7820 7830 7840 7850 7860  
TTCTGTACT TTCTATAGTG AATAGAGTTA GGCAGGGATA TTCACCATTA TCGTTTCAGA

7870 7880 7890 7900 7910 7920  
CCCACCTCCC AACCCTGAGG GGACCTGACA GGCCCGAAGG AATAGAAGAA GAAGGTGGAG

7930 7940 7950 7960 7970 7980  
AGAGAGACAG AGACAGATCC ATTCGATTAG TGAACGGATC CTTAGCACTT ATCTGGGACG

7990 8000 8010 8020 8030 8040  
ATCTGGGGAG CCTTGTGCCT CTTGAGCTAC CACCGCTTGA GAGACTTACT CTTGATTGTA

8050 8060 8070 8080 8090 8100  
ACGAGGATTG TGGAACCTCT GGGACGCAGG GCGTGGGAAG CCCTCAAATA TTGGTGGAAAT

8110 8120 8130 8140 8150 8160  
CTCCTACAGT ATTGGAGTCA GGAACATAAG AATAGTGCTG TTAGCTTGCT CAATGCCACA

8170 8180 8190 8200 8210 8220  
GCCATAGCAG TAGCTGAGGG GACAGATAGG GTTATAGAAG TAGTACAAGG AGCTTGTAGA

8230 8240 8250 8260 8270 8280  
GCTATTCGCC ACATACCTAG AAGAATAAGA CAGGGCTTGG AAAGGATTTT GCTATAAGAT

8290 8300 8310 8320 8330 8340  
GGGTGGCAAG TGGTCAAAAA GTAGTGTGGT TGGATGGCCT ACTGTAAGGG AAAGAATGAG

8350 8360 8370 8380 8390 8400  
ACGAGCTGAG CCAGCAGCAG ATGGGGTGGG AGCAGCATCT CGAGACCTGG AAAAACATGG

8410 8420 8430 8440 8450 8460  
AGCAATCACA AGTAGCAATA CAGCAGCTAC CAATGCTGCT TGTGCCTGGC TAGAAGCACA

8470 8480 8490 8500 8510 8520  
AGAGGAGGAG GAGGTGGGTT TTCCAGTCAC ACCTCAGGTA CCTTTAAGAC CAATGACTTA

8530 8540 8550 8560 8570 8580  
CAAGGCAGCT GTAGATCTTA GCCACTTTTT AAAAGAAAAG GGGGCACTGG AAGGGCTAAT

8590 8600 8610 8620 8630 8640  
TCACTCCCAA CGAAGACAAG ATATCCTTGA TCTGTGGATC TACCACACAC AAGGCTACTT

8650 8660 8670 8680 8690 8700

111476

CCCTGATTGG CAGAACTACA CACCAGGGCC AGGGGTCAQA TATCCA CTGA CTTTGGATG

8710	8720	8730	8740	8750	8760
GTGCTACAAG	CTAGTACCAG	TIGAGCCAGA	TAAGGTAGAA	GAGGCCAATA	AAGGAGAGAA
8770	8780	8790	8800	8810	8820
CACCAGCTTG	TTACACCCTG	TGAGCCTGCA	TGGAATGGAT	GACCCTGAGA	GAGAAGTGTT
8830	8840	8850	8860	8870	8880
AGAGTGGAGG	TTTGACAGCC	GCCTAGCATT	TCATCACCTG	GCCCGAGAGC	TGCATCCGGA
8890	8900	8910	8920	8930	8940
GTA CTTC AAG	AACTGCTGAC	ATCGAGCTTG	CTACAAGGGA	CTTCCGCTG	GGCACITTTCC
8950	8960	8970	8980	8990	9000
AGGGAGGCGT	GGCCTGGGCG	GAAGTGGGGA	GTGGCGAGCC	CTCAGATGCT	GCATATAAGC
9010	9020	9030	9040	9050	9060
AGCTGCTTTT	TGCCTGTACT	GGGTCTCTCT	GGTTAGACCA	GATTTGAGCC	TGGGAGCTCT
9070	9080	9090	9100	0	0
CTGGCTAACT	AGGGAACCCA	CTGCTTAAGC	CTCAATAAAG	CTT	

Fig 2b

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